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(51) International Patent Classification[7]: C07H 15/16, A61K 31/7052, A61P 31/04

(21) International Application Number: PCT/US2003/025820

(22) International Filing Date: 15 August 2003 (15.08.2003)

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(26) Publication Language: English

(30) Priority Data:
60/403,770 15 August 2002 (15.08.2002) US

(71) Applicant (*for all designated States except US*): VICURON PHARMACEUTICALS, INC. [US/US]; 34790 Ardentch Court, Fremont, CA 94555 (US).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): LEWIS, Jason [US/US]; 2939 Kelly Street, Hayward, CA 94541 (US). PATEL, Dinesh, V. [US/US]; 45109 Cougar Circle, Fremont, CA 94539 (US). ANANDAN, Sampath, K. [IN/US]; 41069 Cornac Terrace, Fremont, CA 94539 (US). GORDEEV, Mikhail, F. [US/US]; 5072 Stone Canyon Drive, Castro Valley, CA 94552 (US).

(74) Agent: BUFFINGER, Nicholas, S.; Morrison & Foerster, LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *with amended claims*

(88) Date of publication of the international search report: 24 June 2004
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(15) Information about Correction:
see PCT Gazette No. 40/2004 of 30 September 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LINCOMYCIN DERIVATIVES POSSESSING ANTIBACTERIAL ACTIVITY

(57) Abstract: Novel lincomycin derivatives are disclosed. These lincomycin derivatives exhibit antibacterial activity. As the compounds of the subject invention exhibit potent activities against bacteria, including gram positive organisms, they are useful antimicrobial agents. Methods of synthesis and of use of the compounds are also disclosed.

WO 2004/016632 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/25820

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H15/16 A61K31/7052 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 549 615 A (BIRKENMEYER ROBERT D) 22 December 1970 (1970-12-22) the whole document	1,9
A	US 3 702 322 A (BANNISTER BRIAN) 7 November 1972 (1972-11-07) the whole document	1,9
A	"The Merck Index" 2001, MERCK & CO. , WHITEHOUSE STATION, NJ , XP002271008 Monograph Number 2377	1,9
A	"The Merck Index" 2001, MERCK & CO. , WHITEHOUSE STATION, NJ , XP002271009 Monograph Number 5522	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 2004	26.07.2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/25820

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 (in part) , 2 (in full), 4-11 (in part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1 (in part), 2 (in full), 4-11 (in part)

   A compound of formula 1 of claim 1 where at least one of R2 or R3 is alkyl or cyanoalkyl or R2 and R3 is =CH2, and compositions and methods pertaining thereto (note that the case where R2 or R3 is hydroxy does also fall within this subject due to the proviso's in claim 1).

   ---

2. claims: 1 (in part), 3 (in full), 4-11 (in part)

   A compound of formula 1 of claim 1 where both R2 and R3 are F, and compositions and methods pertaining thereto (note that the case where only one of R2 or R3 is F does fall within the first subject due to the proviso's in claim 1).

   ---

3. claims: 1 (in part), 4-11 (in part)

   A compound of formula 1 of claim 1 where R2 and R3 is =NOR7 with R7 as defined, and compositions and methods pertaining thereto.

   ---

4. claims: 7-11 (in part)

   Compounds summed up in claim 7 not falling within one of the earlier mentioned subjects, and compositions and methods pertaining thereto

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/US 03/25820

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3548615 A	22-12-1970	JP 50016099 B	10-06-1975
		JP 49009506 B	05-03-1974
		DE 1806428 A1	04-06-1969
		FR 1590374 A	13-04-1970
US 3702322 A	07-11-1972	BE 765370 A1	06-10-1971
		CA 945149 A1	09-04-1974
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		CH 554858 A	15-10-1974
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		PH 9506 A	09-01-1976
		SE 385011 B	31-05-1976
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		ZA 7101709 A	26-01-1972

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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 24 June 2004

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Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2004	18. 05. 2004
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer de Nooy, A

INTERNATIONAL SEARCH REPORT

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see additional sheet

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Remark on Protest

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		SE 409209 B	06-08-1979
		ZA 7101709 A	26-01-1972

N-HYDROXYAMIDE DERIVATIVES POSSESSING ANTIBACTERIAL ACTIVITY

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0001] This invention relates to N-hydroxyamide derivatives which inhibit UDP-3-*O*-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC) and as a result, have gram negative antibacterial activity.

[0002] Lipid A is the hydrophobic anchor of lipopolysaccharide (LPS) and forms the major lipid component of the outer monolayer of the outer membrane of gram-negative bacteria. Lipid A is required for bacterial growth and inhibition of its biosynthesis is lethal to the bacteria. Furthermore, blocking Lipid A biosynthesis increases the sensitivity of bacteria to other antibiotics.

[0003] One of the key enzymes of bacterial lipid A biosynthesis is LpxC. LpxC catalyzes the removal of the N-acetyl group of UDP-3-*O*-(R-3-hydroxymyristoyl)-N-acetylglucosamine. The LpxC enzyme is essential in gram negative bacteria for the biosynthesis of Lipid A, and it is notably absent from mammalian genomes. Since LpxC is essential for Lipid A biosynthesis and inhibition of Lipid A biosynthesis is lethal to bacteria, inhibitors of LpxC have utility as antibiotics. In addition, the absence of LpxC from mammalian genomes reduces potential toxicity of LpxC inhibitors in mammals. Accordingly, LpxC is an attractive target for antibacterial drug discovery.

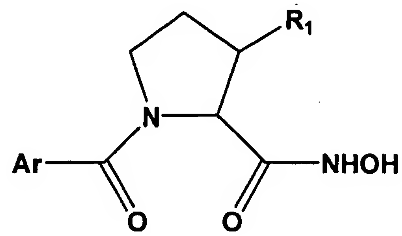
[0004] By way of example, U.S. Patent 5,925,659 teaches that certain heterocyclic hydroxamate compounds, in particular oxazoline compounds, have the ability to inhibit LpxC.

[0005] Accordingly, compounds, which possess LpxC inhibitory activity, are desired as potential antibacterial agents.

SUMMARY OF THE INVENTION

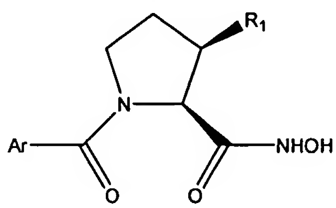
[0006] The present invention provides N-hydroxyamide derivatives which inhibit LpxC and thereby possess gram negative antibacterial activity.

[0007] In one embodiment, antibiotics of this invention include compounds of Formula I:

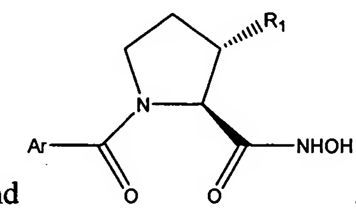


I

wherein R_1 may be N_3, NH_2, $NHSO_2CH_3$, NHCOH, $NHCH_3$, F, or OCH_3; and wherein Ar is an optionally substituted aryl or heteroaryl. Compounds of this invention also include compounds with the following stereochemistry:



and



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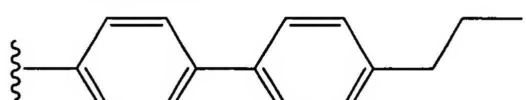
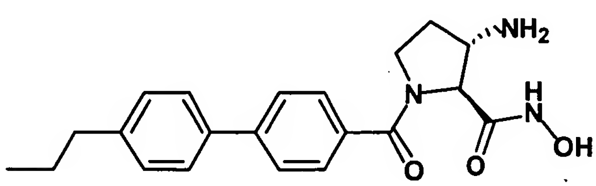
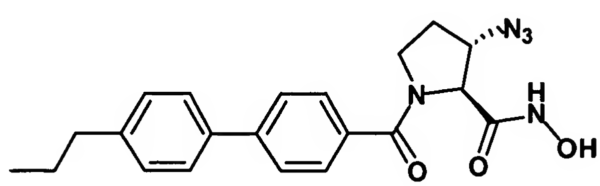
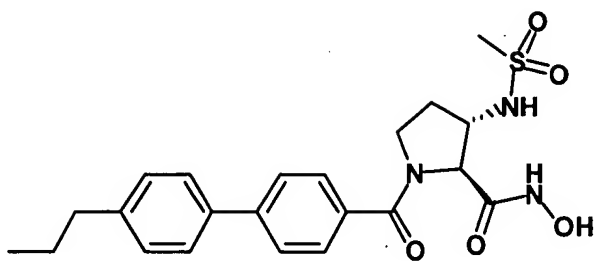
Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may include the following substituted aryl compound.

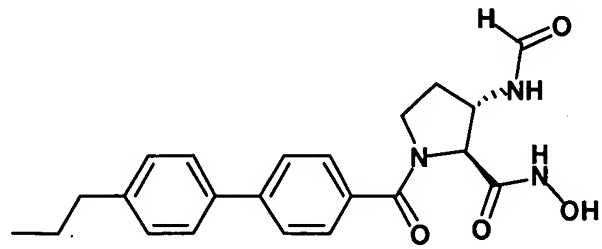


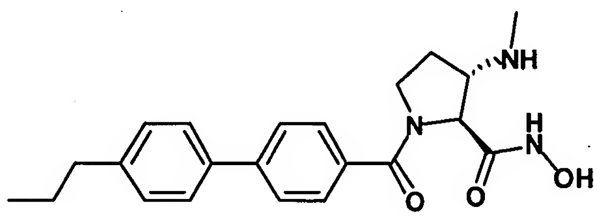
Particularly preferred compounds include the following compounds.

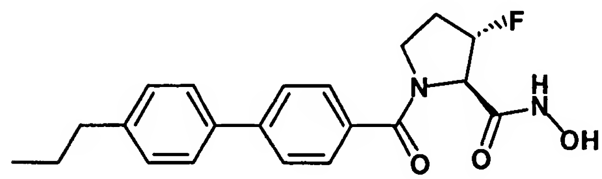


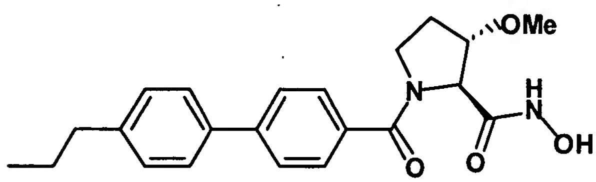


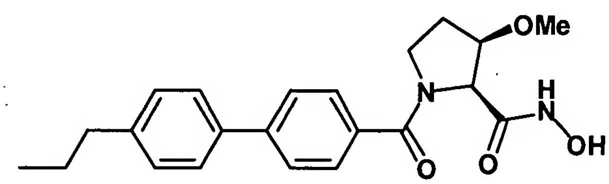




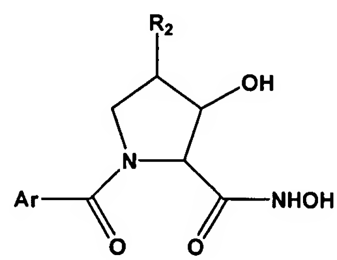






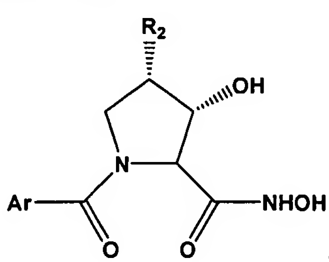


[0008] In another embodiment, antibiotics of this invention include compounds of Formula II:



II

wherein R_2 may be OH or NH_2; and wherein Ar may be an optionally substituted aryl or heteroaryl. Compounds of this invention also include compounds with the following stereochemistry:



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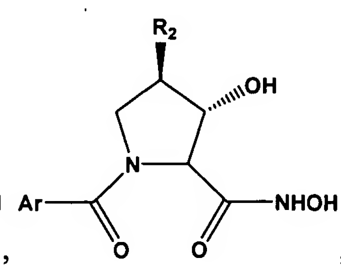
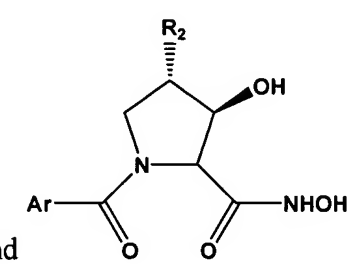


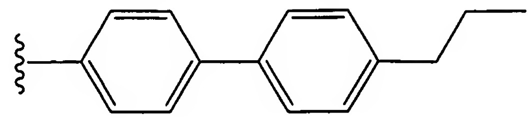
, and



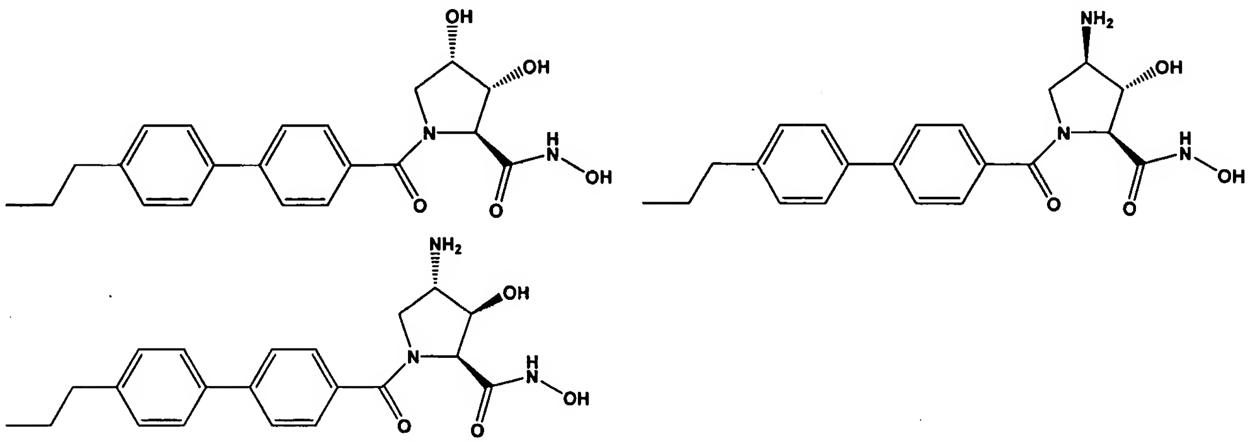
.

NB1:662111.3

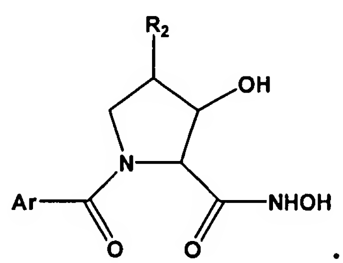
Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compound.



Particularly preferred compounds include the following compounds.

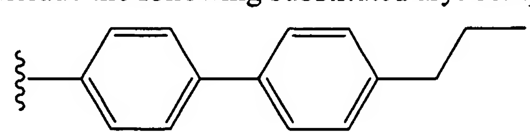


[0009] In another embodiment, antibiotics of this invention include compounds of Formula III:



III

wherein R_1 may be H, N_3, NH_2, $NHSO_2CH_3$, NHCOH, $NHCH_3$, F, OCH_3, or OH; R_2 may be H, OH, or NH_2; R_3 may be H or CH_2OCH_3; and Ar may be an optionally substituted aryl or heteroaryl. Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compound.

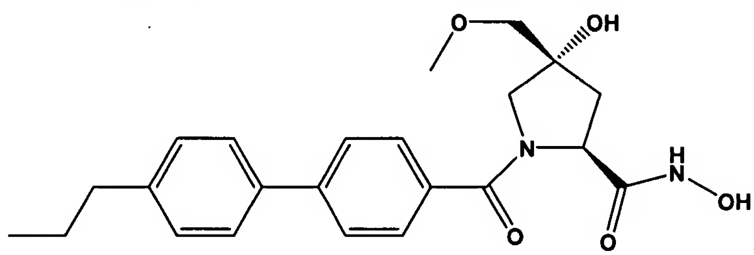


Particularly preferred embodiments also include compounds with the following substituents:

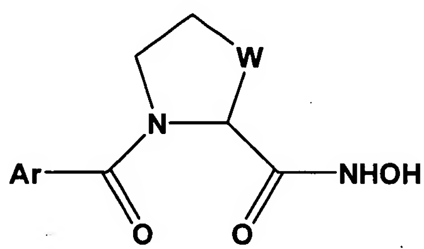
- wherein R_1 is NH_2, R_2 is H, and R_3 is H;

- wherein R_1 is H, R_2 is OH, and R_3 is CH_2OCH_3;
- wherein R_1 is N_3, R_2 is H, and R_3 is H;
- wherein R_1 is $NHSO_2CH_3$, R_2 is H, and R_3 is H;
- wherein R_1 is NHCOH, R_2 is H, and R_3 is H;
- wherein R_1 is $NHCH_3$, R_2 is H, and R_3 is H;
- wherein R_1 is F, R_2 is H, and R_3 is H;
- wherein R_1 is OCH_3, R_2 is H, and R_3 is H;
- wherein R_1 is OH, R_2 is OH, and R_3 is H; and
- wherein R_1 is OH, R_2 is NH_2, and R_3 is H.

Additionally, preferred embodiments also include the compound with the following structure

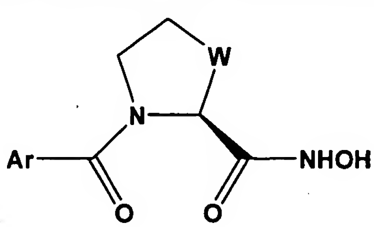


[0010] In another embodiment, antibiotics of this invention include compounds of Formula IV:

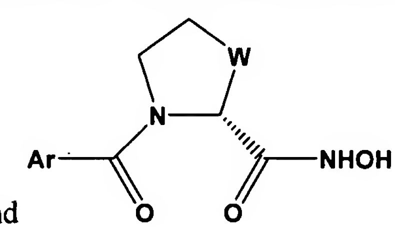


IV

wherein W may be S, SO, or SO_2; and Ar may be an optionally substituted aryl or heteroaryl. Compounds of this invention also include compounds with the following stereochemistry:

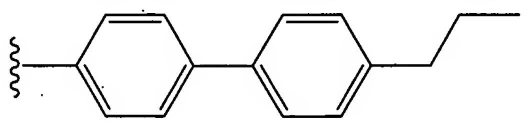


and

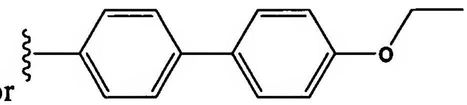


.

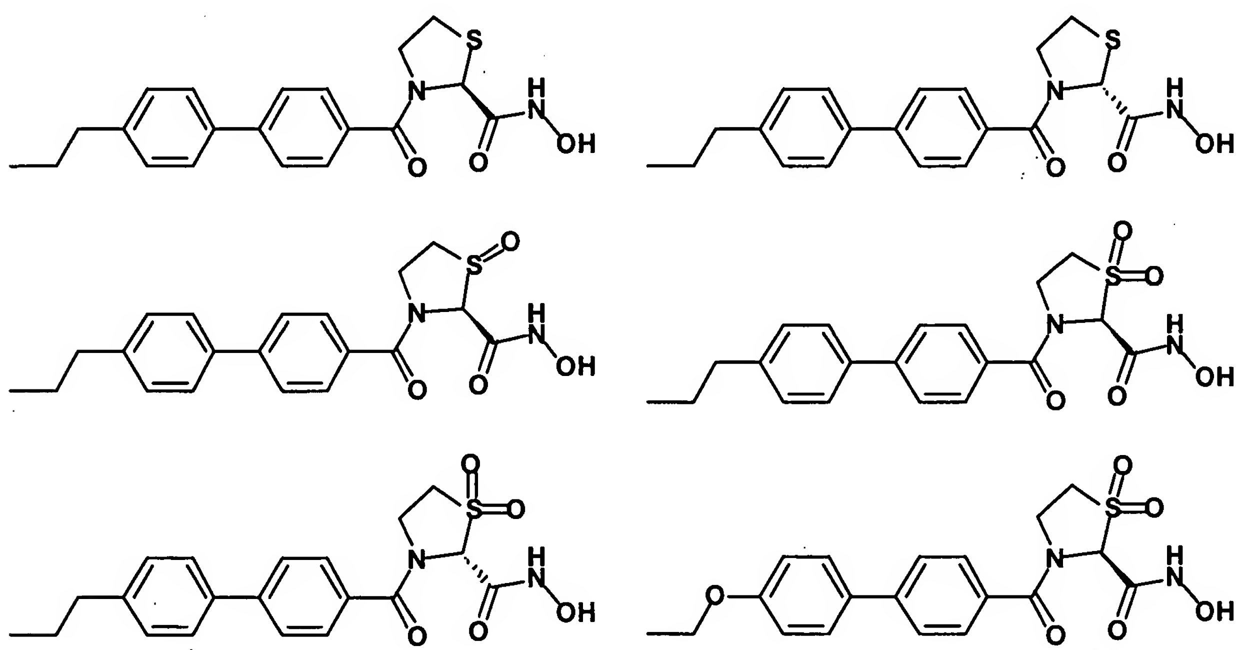
Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compounds.



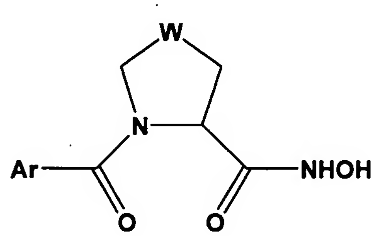
or



Particularly preferred embodiments also include the following compounds.

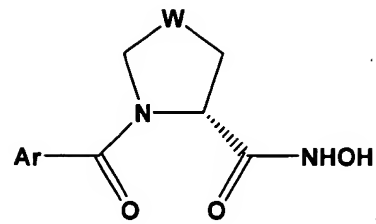


[0011] In another embodiment, antibiotics of this invention include compounds of Formula V:

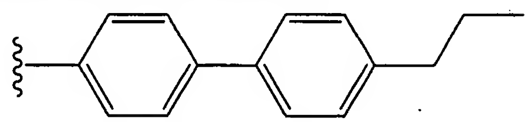


V

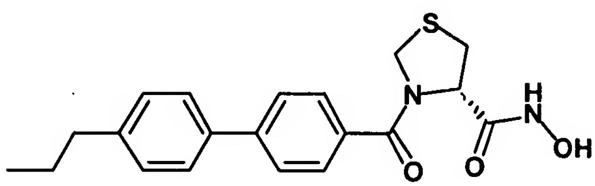
wherein W may be S or SO_2; and Ar may be an optionally substituted aryl or heteroaryl. Compounds of this invention also include a compound with the following stereochemistry:

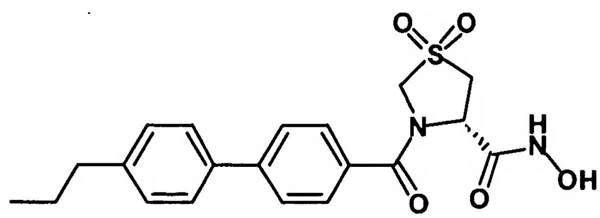


Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compound.

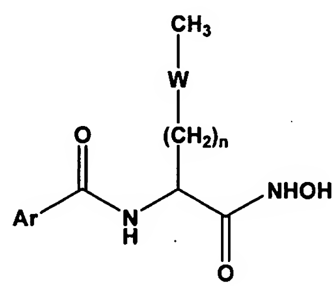


Particularly preferred embodiments also include the following compounds.



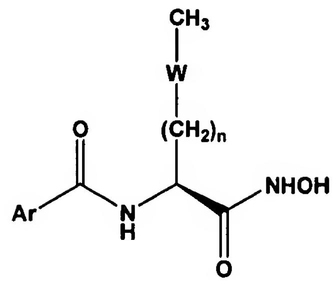


[0012] In another embodiment, antibiotics of this invention include compounds of Formula VI:

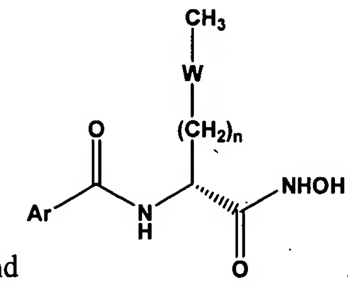


VI

wherein W may be S or SO_2; n is 1 or 2; and Ar may be an optionally substituted aryl or heteroaryl. Compounds of this invention also include compounds with the following stereochemistry:

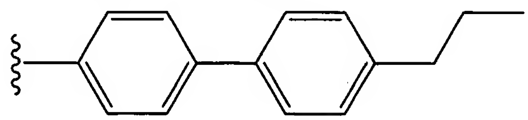


and



.

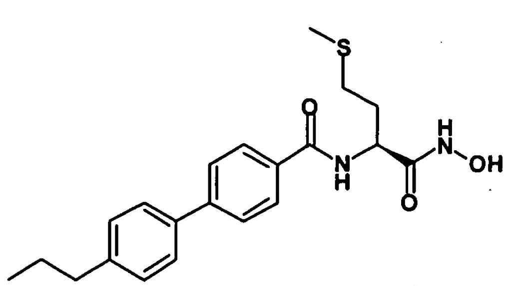
Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compound.

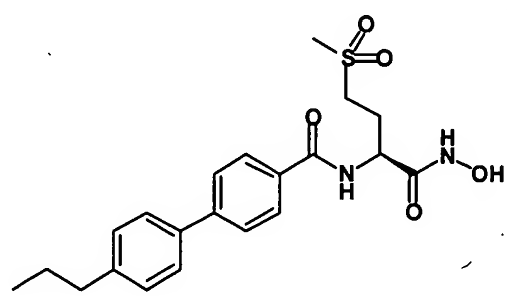


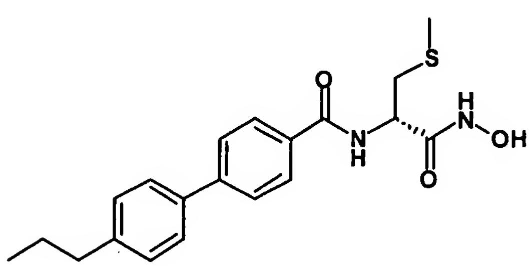
Particularly preferred embodiments also include compounds with the following substituents:

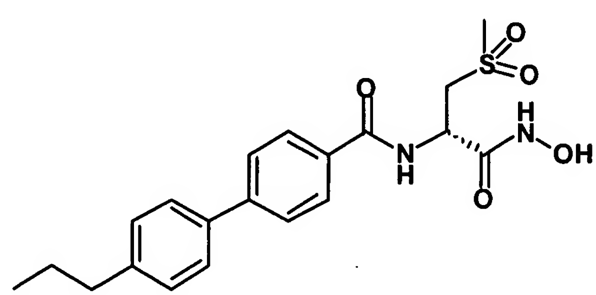
- wherein W is S and n is 1;
- wherein W is S and n is 2;
- wherein W is SO_2 and n is 1; and
- wherein W is SO_2 and n is 2.

Particularly preferred embodiments include the following compounds.

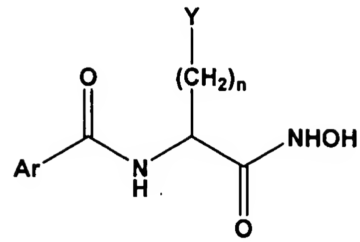






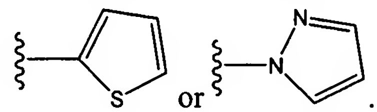


[0013] In another embodiment, antibiotics of this invention include compounds of Formula VII:

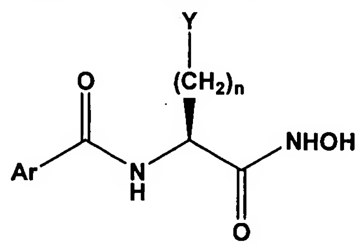


VII

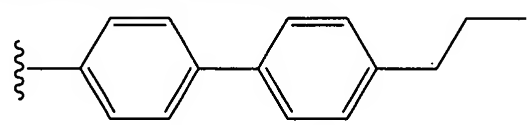
wherein Y is a heteroaryl; n is 0 or 1; and Ar is an optionally substituted aryl or heteroaryl. In one embodiment, Y may be a 5-membered heteroaryl ring. Additionally, Y may be



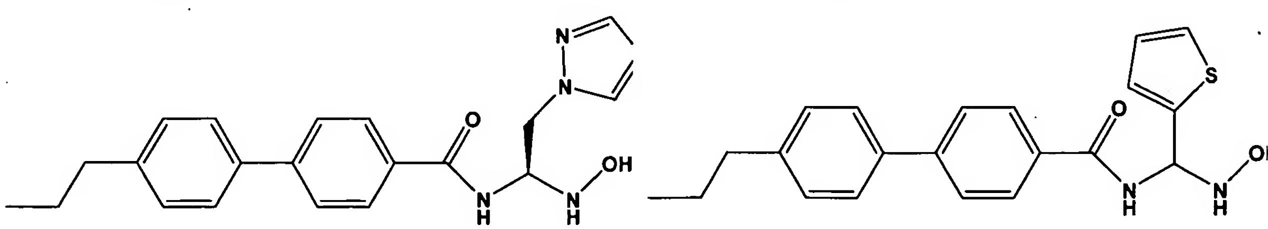
Compounds of this invention also include a compound with the following stereochemistry:



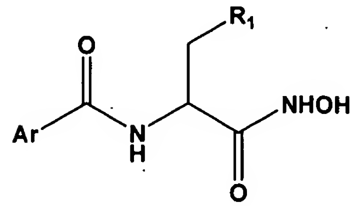
Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compound.



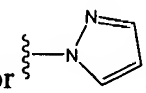
Particularly preferred compounds also include the following compounds.

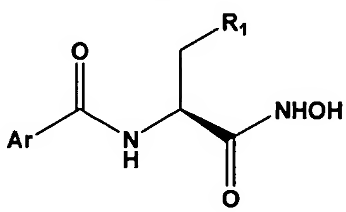


[0014] In another embodiment, antibiotics of this invention include compounds of Formula VIII:

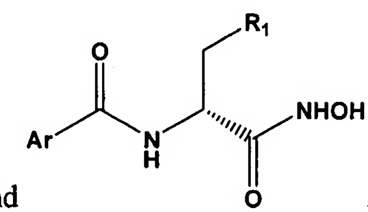


VIII

wherein R_1 may be CH_2SCH_3, $CH_2SO_2CH_3$, SCH_3, SO_2CH_3, or  ; and Ar may be an optionally substituted aryl or heteroaryl. Compounds of this invention also include compounds with the following stereochemistry:

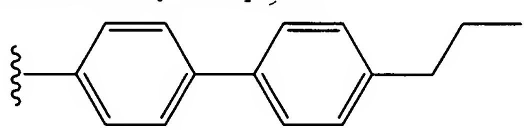


and

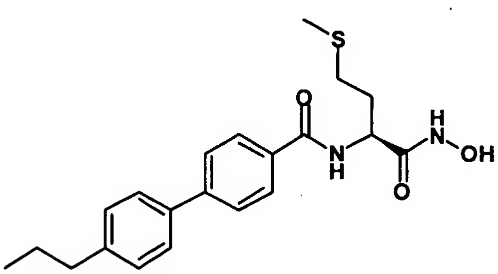


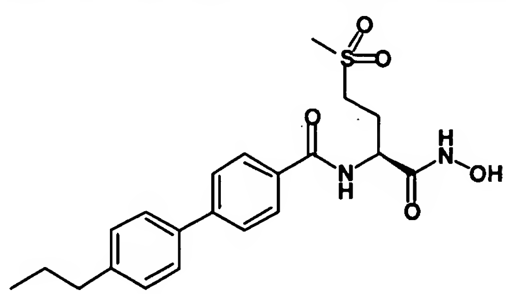
.

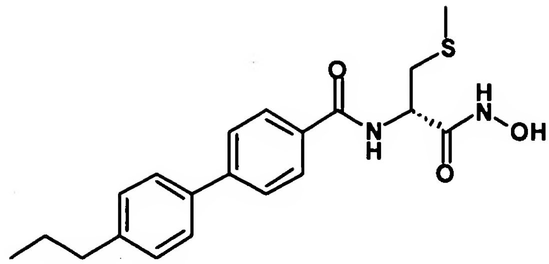
Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compound.

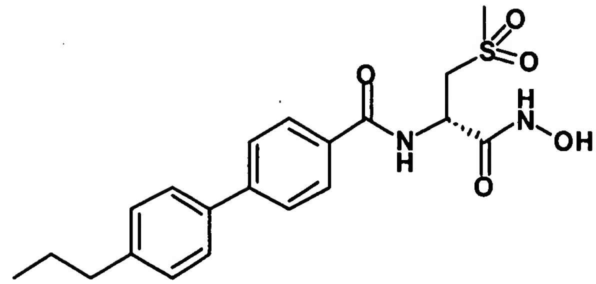


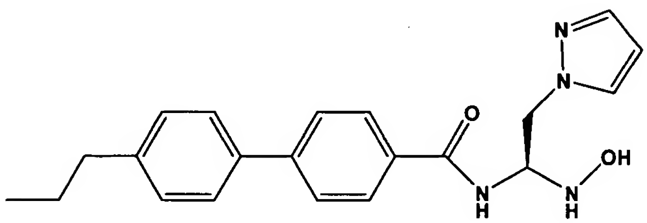
Particularly preferred embodiments also include compounds having the following structures.



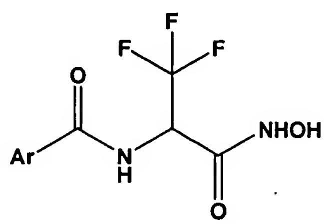






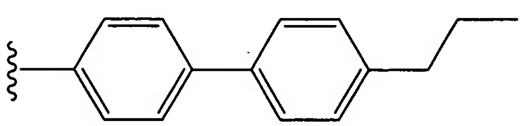
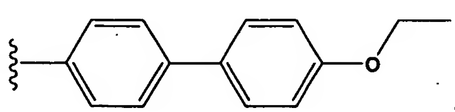


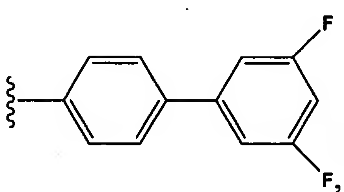
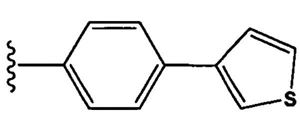
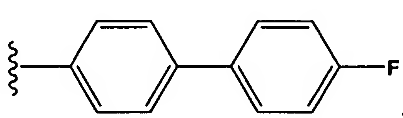
[0015] In another embodiment, antibiotics of this invention include compounds of Formula IX:



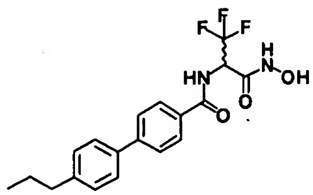
IX

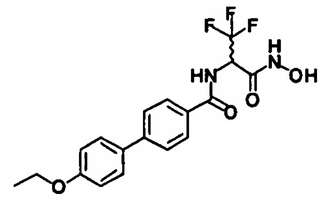
wherein Ar is an optionally substituted aryl or heteroaryl. Ar groups include, but are not limited to,

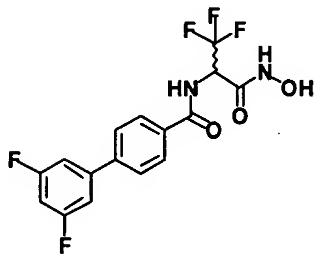
, ,

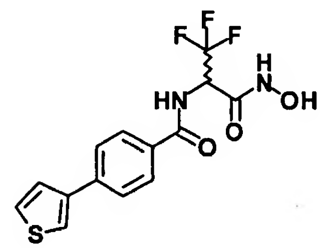
, , and .

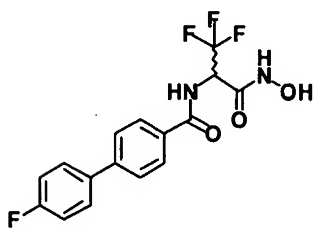
Particularly preferred embodiments of the following invention also include the following compounds.



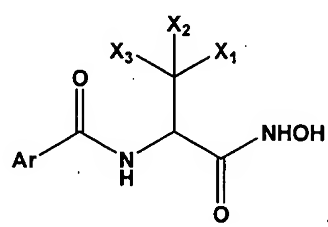






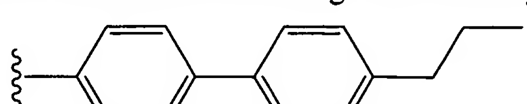


[0016] In another embodiment, antibiotics of this invention include compounds of Formula X:

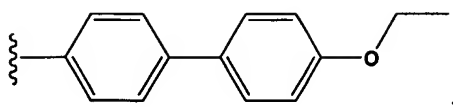
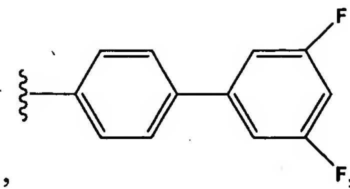
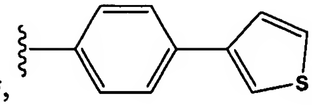
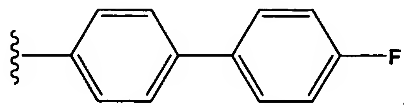


X

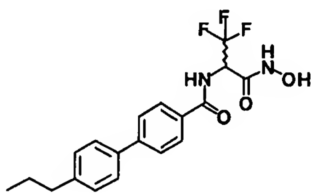
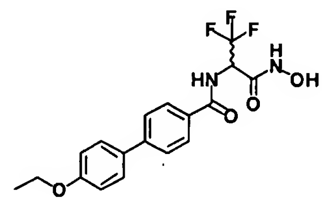
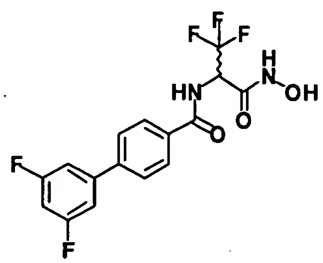
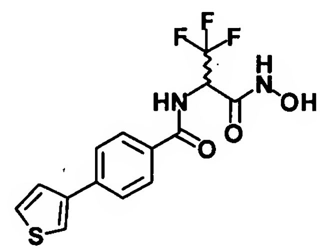
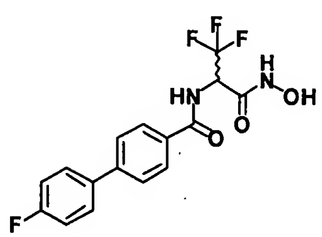
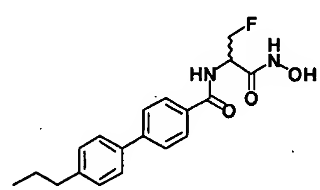
wherein X_1, X_2, and X_3 may each independently be H or F; and Ar may be an optionally substituted aryl or heteroaryl. Although Ar includes any optionally substituted aryl or heteroaryl, in one embodiment, Ar may also include the following substituted aryl compound.



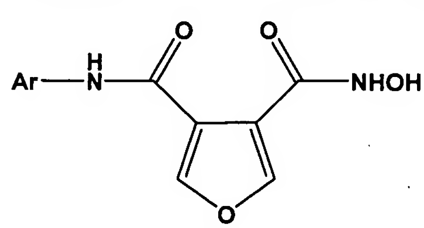
Additionally, Ar groups may be one of the following:

,
,
, or
.

Particularly preferred embodiments of the following invention also include the following compounds.

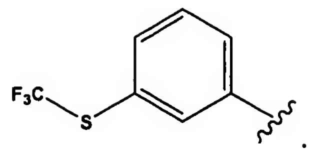







[0017] In another embodiment, antibiotics of this invention include compounds of Formula XI

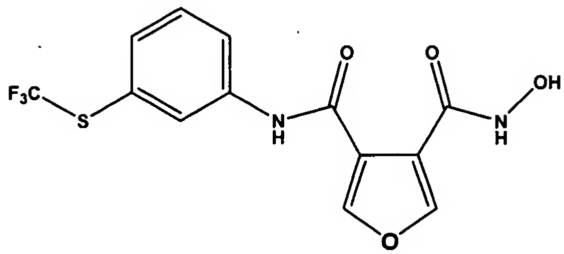


XI

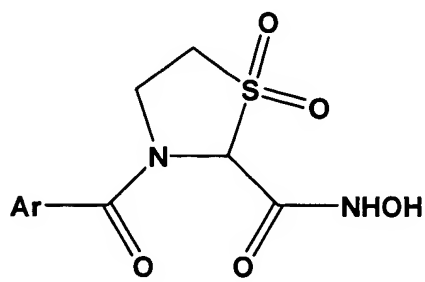
Ar includes any optionally substituted aryl, in one embodiment, Ar may also include the following substituted aryl compound.



Compounds of the present invention also include, but are not limited to, the following structure:

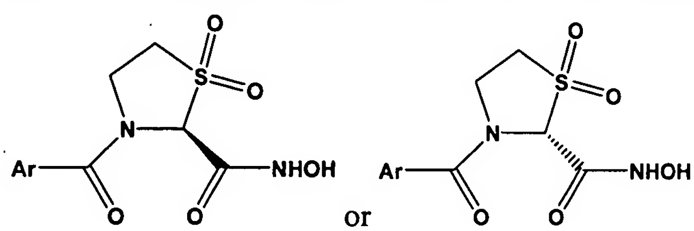


[0018] In another embodiment, antibiotics of this invention include compounds of Formula XII

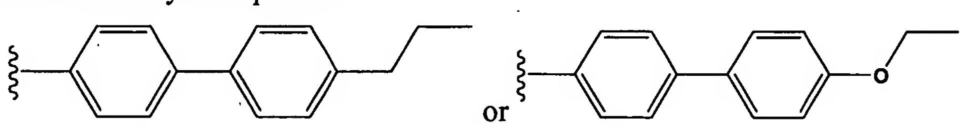


XII

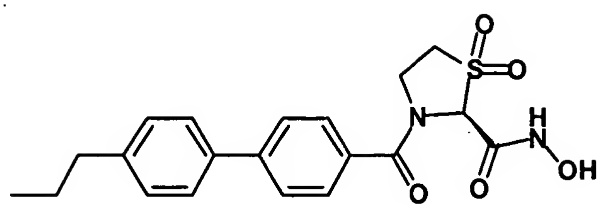
Compounds of this invention also include compounds with the following stereochemistry:

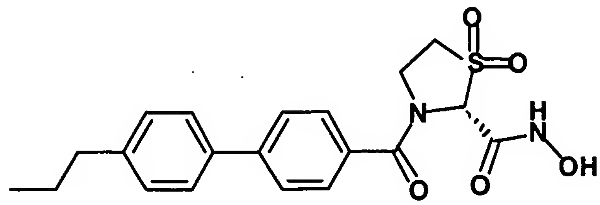


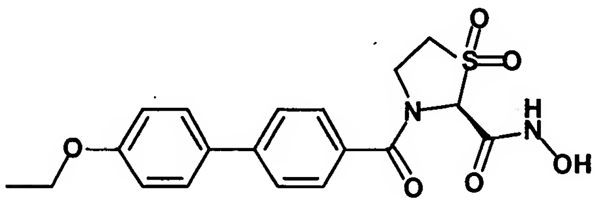
Ar includes any optionally substituted aryl, in one embodiment, Ar may also include the following substituted aryl compounds.



Particularly preferred embodiments also include compounds having the following structures.







[0019] In another aspect, this invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of the compounds defined herein. The pharmaceutical compositions of the present invention may further comprise one or more additional antibacterial agents, one of which may be active against gram positive bacteria. One of which may also be active against gram negative bacteria.

[0020] In one of its method aspects, this invention is directed to a method for the treatment of a microbial infection in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of this invention. The compound of this invention may be administered to the mammal orally, parenterally, transdermally, topically, rectally, or intranasally in a pharmaceutical composition.

[0021] In another of its method aspects, this invention is directed to a method for the treatment of a microbial infection in a mammal comprising administering to the mammal a pharmaceutical composition comprising a therapeutically effective amount of a compound of this invention. The pharmaceutical composition may further one or more additional antibacterial agents, one of which may be active against gram positive bacteria. One of which may also be active against gram negative bacteria.

[0022] The pharmaceutical composition may be administered to the mammal orally, parenterally, transdermally, topically, rectally, or intranasally.

[0023] In a preferred embodiment, the infection is a gram negative infection. In an additional embodiment, the infection may be a gram positive infection.

[0024] In yet another aspect, the present invention provides novel intermediates and processes for preparing the compounds.

DETAILED DESCRIPTION OF THE INVENTION

[0025] As described above, this invention relates to N-hydroxyamide derivatives which inhibit LpxC and as a result, have gram negative antibacterial activity. Other N-hydroxyamide derivatives that also inhibt LpxC were described in U.S. Application Serial Nos. 60/394,862, filed July 12, 2002, and 10/617,616, filed July 11, 2003, the entirety of all of which are hereby expressly incorporated by reference in their entirety. However, prior to describing this invention in further detail, the following terms will first be defined.

Definitions

[0026] Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

[0027] "Halo" means fluoro, chloro, bromo, or iodo.

[0028] "Nitro" means the group $-NO_2$.

[0029] "Hydroxy" means the group -OH.

[0030] "Alkyl" means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to eight carbon atoms. Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, and the like.

[0031] "Alkylene" means a linear divalent hydrocarbon group of one to eight carbon atoms or a branched divalent hydrocarbon group of three to eight carbon atoms. Examples of alkylene groups include, but are not limited to, methylene, ethylene, 2-methylpropylene, and the like.

[0032] "Alkenyl" means a linear unsaturated monovalent hydrocarbon radical of two to eight carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least one double bond, (-C=C-). Examples of alkenyl groups include, but are not limited to, allyl, vinyl, 2-butenyl, and the like.

[0033] "Alkynyl" means a linear monovalent hydrocarbon radical of two to eight carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least one triple bond, (-C≡C-). Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl, 2-butynyl, and the like.

[0034] "Alkynylene" means a linear divalent hydrocarbon radical of two to eight carbon atoms or a branched monovalent hydrocarbon radical of three to eight carbon atoms containing at least one triple bond, (-C≡C-). Examples of alkynylene groups include, but are not limited to, ethynylene, propynylene, and the like.

[0035] "Alkylsilylalkynyl" means the group $(alkyl)_3Si$-alkynylene- where alkyl and alkynylene are as defined above.

[0036] "Haloalkyl" means an alkyl substituted with one or more, preferably one to 6, of the same or different halo atoms. Examples of haloalkyl groups include, for example, trifluoromethyl, 3-fluoropropyl, 2,2-dichloroethyl, and the like.

[0037] "Hydroxyalkyl" refers to an alkyl substituted with one or more -OH groups provided that if two hydroxy groups are present they are not both on the same carbon atom. Examples of

hydroxyalkyl groups include, for example, hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, and the like.

[0038] "Alkylthio" refers to the group "alkyl-S-" where alkyl is as defined above and which includes, by way of example, methylthio, butylthio, and the like.

[0039] "Alkylsulfinyl" refers to the group "alkyl-S(O)-" where alkyl is as defined above and which includes, by way of example, methyl-S(O)-, butyl-S(O)-, and the like.

[0040] "Alkylsulfonyl" refers to the group "alkyl-S(O)$_2$-" where alkyl is as defined above and which includes, by way of example, methyl-S(O)$_2$-, butyl-S(O)$_2$-, and the like.

[0041] "Alkoxy" refers to the group "alkyl-O-", wherein alkyl is as defined above, and which includes, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

[0042] "Alkoxyalkyl" refers to the group "-alkylene-O-alkyl" where alkylene and alkyl are as defined herein and which includes, by way of example, 2-propoxyethylene, 3-methoxybutylene, and the like.

[0043] "Alkenoxy" refers to the group "alkenyl-O-" where alkenyl is as defined herein and which includes, by way of example, allyloxy, vinyloxy, 2-butenyloxy, and the like.

[0044] "Alkenoxyalkyl" refers to the group "alkenyl-O-alkylene" where alkenyl and alkylene are as defined herein and which includes, by way of example, 3-allyloxy-propylene, 2-(2-propenyloxy)ethylene, and the like.

[0045] "Alkynyloxy" refers to the group "alkynyl-O-" where alkynyl is as defined herein and which includes, by way of example, propargyloxy and the like.

[0046] "Arylalkoxyalkyl" refers to the group "aryl-alkoxy-alkylene-" whre aryl, alkoxy and alkylene are as defined herein.

[0047] "Haloalkoxy" refers to the group "haloalkyl-O-" where haloalkyl is as defined herein and which includes, by way of example, trifluoromethoxy, 2,2-dichloroethoxy, and the like.

[0048] "Haloalkylthio" refers to the group "haloalkyl-S-" where haloalkyl is as defined herein and which includes, by way of example, trifluoromethylthio, 2,2-difluoropropylthio, 3-chloropropylthio, and the like.

[0049] "Haloalkyl-sulfinyl" refers to the group "haloalkyl-S(O)-" where haloalkyl is as defined herein and which includes, by way of example, trifluoromethanesulfinyl, 2,2-dichloroethanesulfinyl, and the like.

[0050] "Haloalkyl-sulfonyl" refers to the group "haloalkyl-$S(O)_2$-" where haloalkyl is as defined herein and which includes, by way of example, trifluoromethanesulfinyl, 2,2-dichloroethanesulfinyl, and the like.

[0051] "Amino" refers to the group "-NR_aR_b" wherein R_a and R_b are independently H, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl where each of alkyl, haloalkyl, alkenyl, cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl are as defined herein.

[0052] "Carbonyl" means the group "-C(O)-."

[0053] "Carboyxl" refers to –COOR where R is hydrogen, alkyl, aryl, heteroaryl and heterocycle or salts thereof.

[0054] "Carboxylamide" refers to –C(O)NR$_a$R$_b$" wherein R$_a$ and R$_b$ are independently H, alkyl, haloalkyl, alkenyl, cycloalkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl where each of alkyl, haloalkyl, alkenyl, cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl are as defined herein.

[0055] "Acyloxy" means the group -C(O)R' wherein R' is alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl where alkyl, alkenyl, alkynyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl are as defined herein.

[0056] "Cycloalkyl" means a cyclic saturated hydrocarbon group of 3 to 8 ring atoms, where one or two of C atoms are optionally replaced by a carbonyl group. The cycloalkyl group may be optionally substituted with one, two, or three substituents, preferably alkyl, alkenyl, halo, hydroxyl, cyano, nitro, alkoxy, haloalkyl, alkenyl, and alkenoxy as these terms are defined herein. Representative examples include, but are not limited to, cyclopropyl, cyclohexyl, cyclopentyl, and the like.

[0057] "Cycloalkylalkyl" means a group -R$_c$R$_d$ where R$_c$ is an alkylene group and R$_d$ is a cycloalkyl group, as defined above. Examples include, but are not limited to, cyclopropylmethylene, cyclohexylethylene, and the like.

[0058] "Aryl" means a monovalent monocyclic or bicyclic aromatic carbocyclic group of 6 to 14 ring atoms. Examples include, but are not limited to, phenyl, naphthyl, and anthryl. The aryl ring may be optionally fused to a 5-, 6-, or 7-membered monocyclic non-aromatic ring optionally containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen, or sulfur, the remaining ring atoms being C where one or two C atoms are optionally replaced by a carbonyl. Such fused ring systems are referre to herein as "cyclic moiety containing a total of 4, 5, 6, or 7

ring atoms." Representative aryl groups with fused rings include, but are not limited to, 2,5-dihydro-benzo[*b*]oxepine, 2,3-dihydrobenzo[1,4]dioxane, chroman, isochroman, 2,3-dihydrobenzofuran, 1,3-dihydroisobenzofuran, benzo[1,3]dioxole, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydroquinoline, 2,3-dihydro-1Hindole, 2,3-dihydro1H-isoindle, benzimidazole-2-one, 2-H-benzoxazol-2-one, and the like.

[0059] "Substituted aryl" means an aryl ring substituted with one or more substituents, preferably one to three substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, alkoxy, acyloxy, amino, hydroxyl, carboxy, cyano, nitro, and alkylthio as these terms are defined herein. The aryl ring may be optionally fused to a 5-, 6-, or 7-membered monocyclic non-aromatic ring optionally containing 1 or 2 heteroatoms independently selected from oxygen, nitrogen, or sulfur, the remaining ring atoms being C where one or two C atoms are optionally replaced by a carbonyl.

[0060] "Heteroaryl" means a monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. Representative examples include, but are not limited to, thienyl, benzothienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, quinoxalinyl, imidazolyl, furanyl, benzofuranyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, 2-pyridonyl, 4-pyridonyl, N-alkyl-2-pyridonyl, pyrazinonyl, pyridazinonyl, pyrimidinonyl, oxazolonyl, and the like.

[0061] "Substituted heteroaryl" means a heteroaryl ring substituted with one or more substituents, preferably one to three substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, alkoxy, acyloxy, amino, hydroxyl, carboxy, cyano, nitro, and alkylthio as these terms are defined herein.

[0062] "Aryloxy" means a group "-O-Ar" where Ar is an aryl group or substituted aryl group as these terms are defined herein. Examples include, but are not limited to, benzyloxy, 4-trifluoromethyl-benzyloxy, and the like.

[0063] "Arylalkoxy" means a group "-O-alkylene-Ar" where Ar is an aryl group or substituted aryl group as defined herein and alkylene is as also defined herein. Examples include, but are not limited to, 2-(phenyl)ethoxy, 3-(phenyl)propoxy, and the like.

[0064] "Arylalkoxyalkyl" means a group "-alkylene-O-alkylene-Ar" where Ar is an aryl group or substituted aryl group as defined herein and each alkylene is independently selected from the other, wherein alkylene is as also defined herein. Examples include, but are not limited to, benzyloxy-propylene, benzyloxy-ethylene, and the like.

[0065] "Aminocarboxyalkyl" means a group "-$R_cC(O)NR_aR_b$" where R_c is an alkylene group as defined herein and R_a and R_b are as defined above.

[0066] "Haloarylalkyl" means the group "aryl-alkylene-" having 1 to 6 halo substituents on either the aryl and/or the alkylene groups where aryl and alkylene are as defined herein.

[0067] "Haloarylalkenyl" means the group "aryl-alkenylene-" having 1 to 6 halo substituents on either the aryl and/or the alkenylene groups where aryl and alkenylene are as defined herein.

[0068] "Haloarylalkynyl" means the group "aryl-alkynylene-" having 1 to 6 halo substituents on either the aryl and/or the alkynylene groups where aryl and alknyylene are as defined herein.

[0069] "Heterocycle" or "heterocyclic" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 10 carbon atoms and from 1 to 4 heteroatoms selected from the group consisting of nitrogen, sulfur, or oxygen within the ring, wherein, in

fused ring systems one or more of the rings can be aryl or heteroaryl as defined herein. Examples of heterocycles and heteroaryls include, but are not limited to, azetidine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, dihydroindole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, phthalimide, 1,2,3,4-tetrahydro-isoquinoline, 4,5,6,7-tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene, morpholinyl, thiomorpholinyl (also referred to as thiamorpholinyl), piperidinyl, pyrrolidine, tetrahydrofuranyl, and the like.

[0070] Heterocycles may be optionally substituted with from one to three substituents selected from the group consisting of alkyl, alkenyl, alkynyl, halo, alkoxy, acyloxy, amino, hydroxyl, carboxy, cyano, nitro, and alkylthio as these terms are defined herein.

[0071] "Optional" or "optionally" means that the subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "aryl group optionally mono- or di- substituted with an alkyl group" means that the alkyl may but need not be present, and the description includes situations where the aryl group is mono- or disubstituted with an alkyl group and situations where the aryl group is not substituted with the alkyl group.

[0072] A "pharmaceutically acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

[0073] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0074] "Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[0075] A "therapeutically effective amount" means the amount of a compound or mixture of compounds that, when administered to a mammal for treating a disease, is sufficient to effect

such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0076] "Pro-drugs" mean any compound which releases an active parent drug according to a compound of the subject invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the subject invention are prepared by modifying functional groups present in a compound of the subject invention in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of the subject invention wherein a hydroxy, sulfhydryl or amino group in the compound is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to C_1-C_{10} esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-alkylaminocarbonyl) of hydroxy functional groups in compounds of the subject invention, and the like.

[0077] The term "tautomers" refers to herein as a constitutional isomer in which migration of a hydrogen atom results in two ore more structures. As an example of one potential tautomer, the N-hydroxyamide may tautomerize to form a 1,2-dihydroxyimine.

[0078] The term "mammal" refers to all mammals including humans, livestock, and companion animals.

[0079] The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used (e.g. "Ph" for phenyl, "Me" for methyl, "Et" for ethyl, "h" for hour or hours and "rt" for room temperature).

<u>General Synthetic Schemes</u>

[0080] Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

[0081] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Toranto Research Chemicals (North York, ON Canada), Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemie, or Sigma (St. Louis, Missouri, USA) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

[0082] As it will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups, as well as suitable conditions for protecting and deprotecting particular function groups are well known in the art. For example, numerous protecting groups are described in T.W. Greene and G.M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

[0083] The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0084] The compounds of this invention will typically contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers. All such stereoisomers (and enriched mixtures) are included within the scope of this invention, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using,

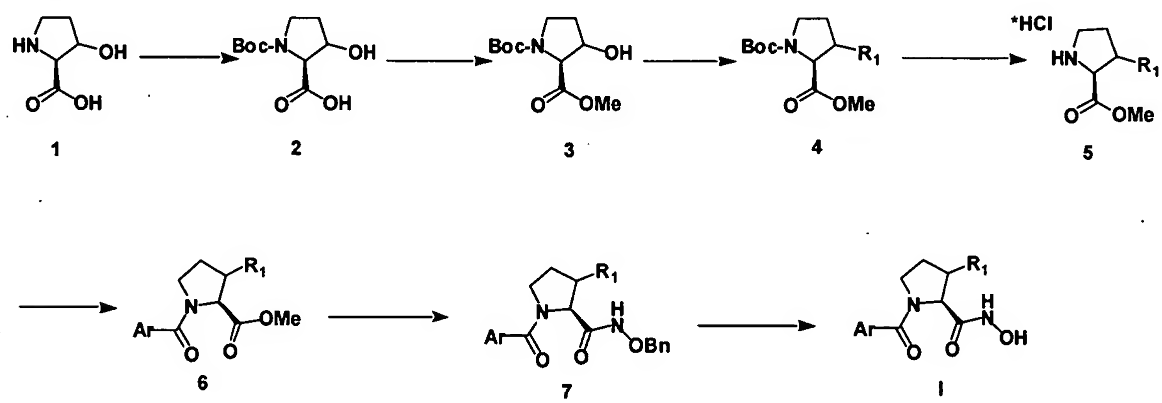
for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

General Synthetic Description

[0085] Compounds of this invention can be prepared by the methods as described below in a way of example.

[0086] Compounds of Formula (I) can be prepared by methods well known in the art of organic chemistry. Representative synthetic procedures for preparing compounds of the present invention are illustrated and described in detail below.

Scheme 1



[0087] As shown in Scheme 1, 3-hydroxyproline is reacted with di-*t*-butyldicarbonate (Boc_2O) in the presence of an organic base to provide a Boc-protected amino acid (2). The transformation is typically carried out in an inert organic solvent, such as dioxane, tetrahydrofuran (THF), and the like, at low temperatures, e.g., 0°C. Suitable organic bases include triethylamine (TEA), pyridine, and suitable inorganic bases include sodium bicarbonate, sodium carbonate, sodium hydroxide the like.

[0088] Me ester of Boc-protected hydroxyproline carboxylic acid (3) can be generated by alkylation with a suitable methylating reagent such as TMS-diazomethane. transformation is

typically carried out at low temperatures, e.g., 0°C, and after the addition, the reaction is allowed to warm to ambient temperatures, e.g., about 25°C.

[0089] Compound 3 can be converted to a variety of other proline derivatives. For example, inversion of the 3-R-hydroxy substituent to the 3-S-hydroxy substituent in compound 3 can be accomplished by reaction with *p*-nitrobenzoic acid, phosphine and DIAD in a suitable solvent such as tetrahydrofuran, dioxane, and alike followed by deacylation with a suitable alkaline reagent such as LiOH in MeOH.

[0090] Reaction of 3-mesylate derivative of 3 (4: R1 = OMs) made e.g., by reacting 3 with MsCl and TEA) with sodium azide in methanol affords respective 3-azido derivatives (4: $R_1 = N_3$) that can be further elaborated into 3-amino compounds ($R_1 = NH_2$). This transformation cab be optionally performed in the presence of a suitable crown ether, e.g., 15-crown-5.

[0091] The N-protected 3-hydroxyproline methyl ester, compound 3, can be used to prepare a variety of further derivatives. For example, reaction with fluorinated reagents (e.g., dimethoxyDAST) followed by deprotection provides for 3-fluoroproline methyl ester (4: R_1 = F). Alternatively, alkylation of the hydroxyl group followed by nitrogen deprotection yields the 3-alkoxyproline methyl ester.

[0092] The substituted proline methyl ester 4 is then treated with an acid to remove the t-butoxycarbonyl protecting group (Boc) and produce the salt 5. Removal of the protecting group may be carried out with acids, such as a trifluoroacetic acid (TFA), hydrochloric acid, *p*-toluenesulfonic acid, and alike, in an inert organic solvent such as dichloromethane, dioxane, THF, and the like. The deprotection is typically conducted at low to ambient temperatures(e.g., 0°C – r.t.).

[0093] The salt 5 is then condensed with an optionally substituted aromatic carboxylic acids under reactive conditions, preferably in an inert organic solvent, in presence of a coupling reagent and an organic base to provide an amide (6) (Scheme 1). Wide range of aromatic acids can be employed, e.g. biaryl carboxylic acid, or substituted biaryl carboxylic acid, etc. This

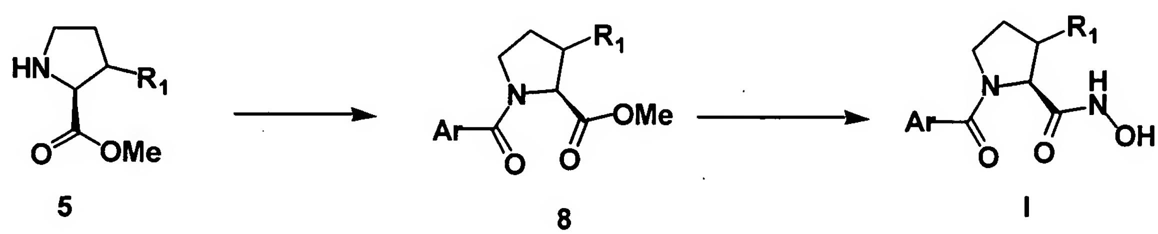
reaction can be performed with any number of known coupling reagents, such as HATU, HOBT, carbodiimides, DPPA, and alike. Suitable organic bases include DIEA, TEA, pyridine, N-methyl morpholine, and alike. Suitable inert organic solvents which can be used include, for example, N,N-dimethylformamide, acetonitrile, dichloromethane, and alike. This reaction is typically carried out at temperatures in the range of about 0°C to about 50°C. The reaction is continued until completion, which typically occurs in from about 2 to 12 hours.

[0094] Compound (6) is then converted to the N- benzyloxyamide derivative (7) by treatment with O-benzyl hydroxylamine and trimethyl aluminium in a non-polar organic solvent such as toluene, methylene chloride and the like (Scheme 1). The reaction is carried out at ambient temperature to 80°C for about 2 to 24 hours.

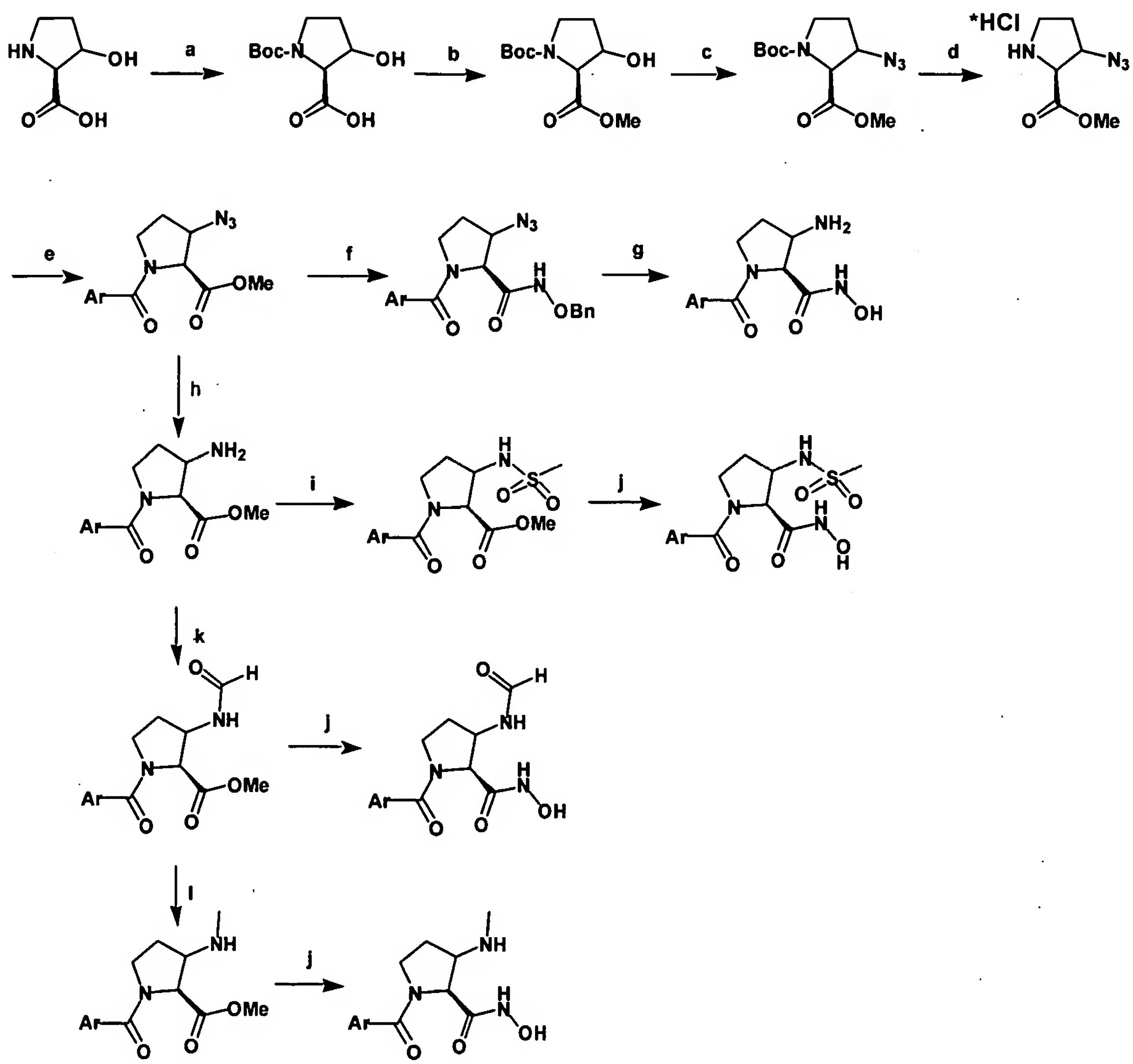
[0095] Compound (7) is then converted to the N-hydroxyamide derivative of Formula (I) by hydrogenation to remove the benzyloxy protecting group (OBz) (Scheme 1). Deprotection is carried out in a polar organic solvent such as methanol. The hydrogenation is carried out at in the presence of a palladium (II) catalyst or palladium on carbon under hydrogen atmosphere. The hydrogenation conveniently may be carried at ambient temperatures in about 1 hour to 16 hours.

[0096] Alternatively, methyl ester 6 can be directly converted into the hydroxamate 7 with a hydroxylamine reagent, such as aq. hydroxylamine, or methanolic hydroxylamine HCl with NaOMe (see Scheme 2 below). The reaction is carried out at ambient temperature for about 2 to 6 hours.

Scheme 2

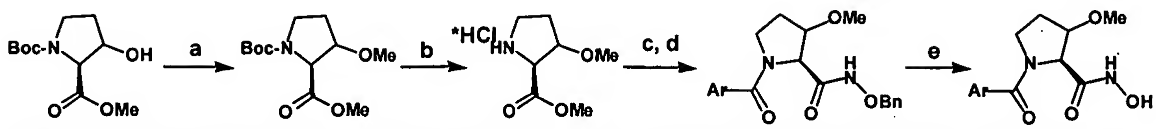


[0097] Synthesis of additional 3-substituted proline derivatives is illustrated by Schemes A-C below.

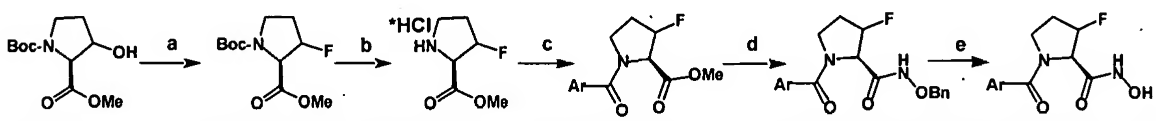


14 15

[0098] **Scheme A.** Reagents and conditions. (a) Protection (Boc_2O, base); (b) Methyl ester formation ($TMSCHN_2$, MeOH); (c) Azide substitution (DPPA, DIAD, Ph_3P); (d) Deprotection (4M HCl/Dioxane); (e) Coupling (ArCOOH, HATU, DIEA, DMF); (f) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (g) Hydroxamate formation (10% Pd/C, H_2, EtOH); (h) Reduction (10% Pd/C, H_2, EtOH). (i) Sulfonamidation (CH_3SO_2Cl, Pyridine); (j) Hydroxamate formation (NH_2OH.HCl, NaOMe, MeOH). (k) N-Formylation (HCOOH, Ac_2O); (l) Reduction ($BH_3.(CH_3)_2S$, THF, MeOH).

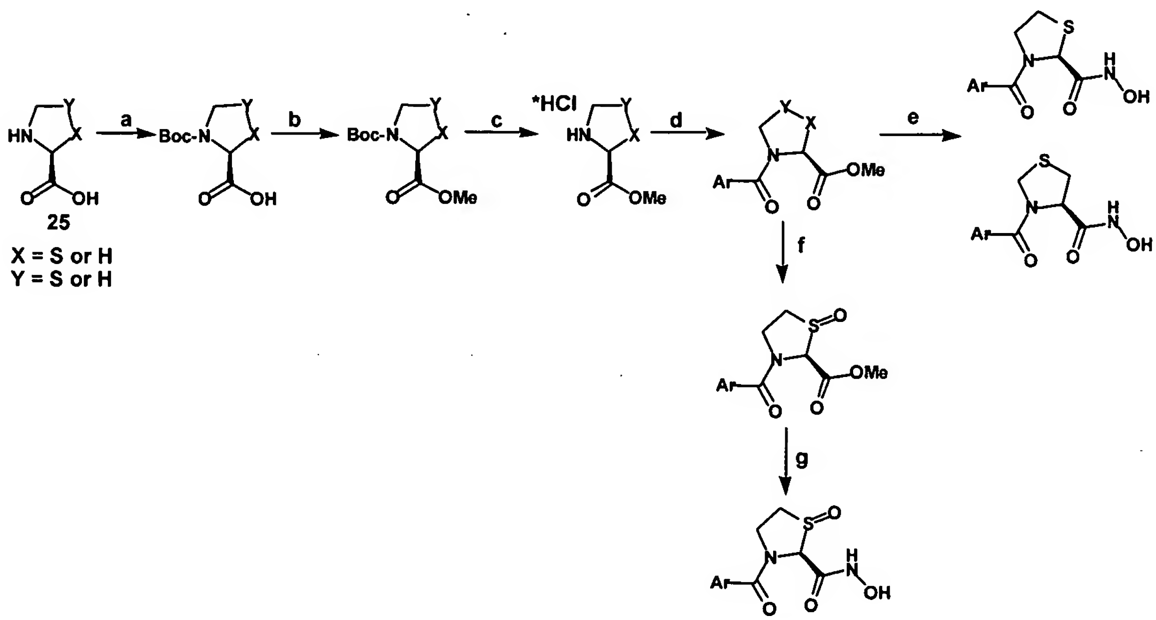


[0099] Scheme B: Reagents and conditions. (a) O-Alkylation ($TMSCHN_2$, MeOH); (b) Deprotection (4M HCl/Dioxane); (c) Coupling (ArCOOH, HATU, DIEA, DMF); (d) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (e) Hydroxamate formation (10% $Pd(OH)_2$/C, EtOH).

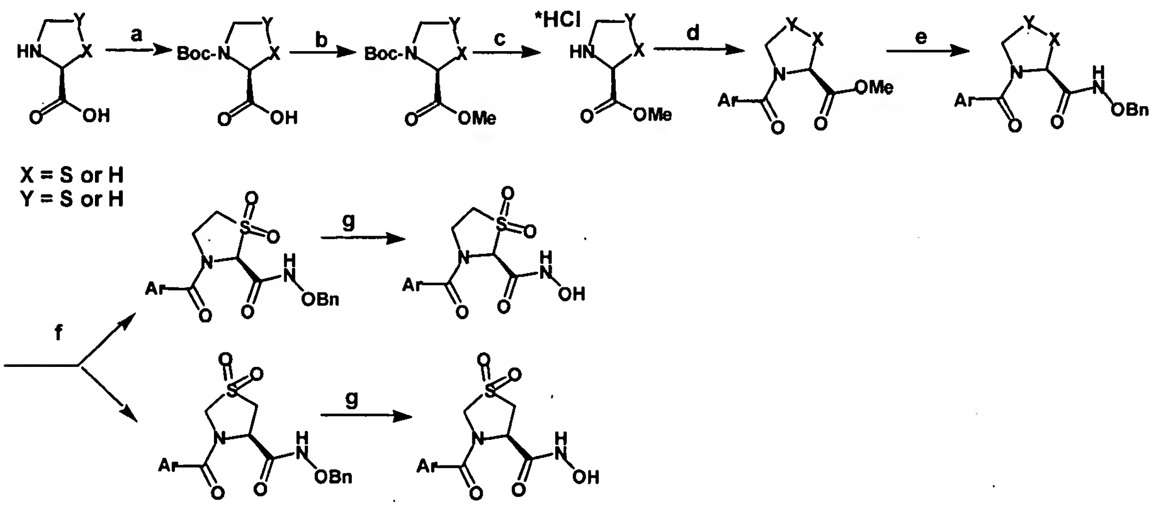


[00100] **Scheme C:** Reagents and conditions. (a) Fluroine substitution (DAST, DCM); (b) Deprotection (4M HCl/Dioxane); (c) Coupling (ArCOOH, HATU, DIEA, DMF); (d) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (e) Hydroxamate formation (10% $Pd(OH)_2$/C, EtOH).

General syntheses of 1-Aroyl Thiazolidinesulfone Hydroxamate Derivatives is illustrated by Schemes D and E below.

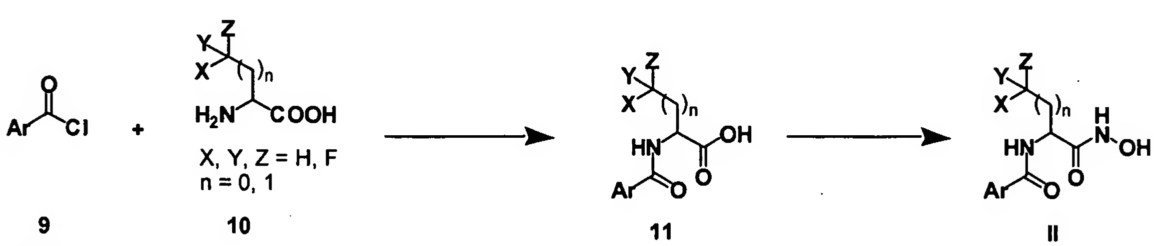


[00101] **Scheme D:** Reagents and conditions. (a) Protection (Boc_2O, base); (b) Methyl ester formation ($TMSCHN_2$, MeOH); (c) Deprotection (4M HCl/Dioxane); (d) Coupling (ArCOOH, HATU, DIEA, DMF); (e) Hydroxamate formation ($NH_2OH.HCl$, NaOMe, MeOH); (f) Oxidation (MCPBA, DCM); (g) Hydroxamate formation (50% NH_2OH, KCN(cat.), MeOH).



[00102] **Scheme E:** Reagents and conditions. (a) Protection (Boc_2O, base); (b) Methyl ester formation ($TMSCHN_2$, MeOH); (c) Deprotection (4M HCl/Dioxane); (d) Coupling (ArCOOH, HATU, DIEA, DMF); (e) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (f) Oxidation (MCPBA, DCM); (g) Hydroxamate formation (10% $Pd(OH)_2$, EtOH).

[00103] Scheme 3 below illustrate methods for preparing compounds Formula II.



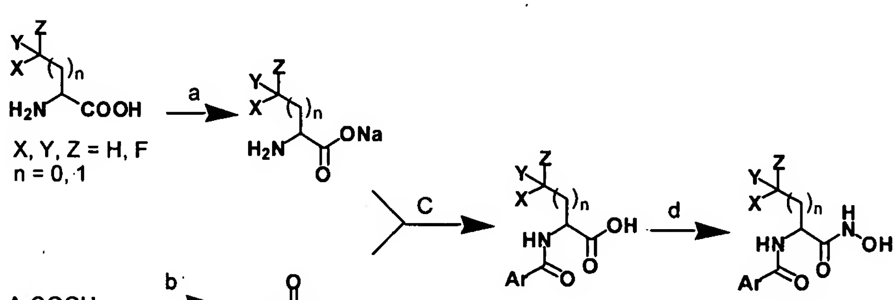
Scheme 3

[00104] As shown in Scheme 3, to an aromatic acyl chloride (commercial or generated from respective carboxylic acid, e.g., with oxalyl chloride and catalytic DMF) is reacted with the

amino acid (10) is in a mixture of organic solvent and water in the presence of inorganic base to provide a amide (11). Suitable inorganic bases include sodium hydroxide, sodium bicarbonate, and the like. Suitable inert organic solvents include dichloromethane, THF, and the like. The reaction conveniently may be conducted at ambient temperature in about 30 minutes to 2 hours.

[00105] Me ester of N-acyl amino acid (11) can be generated by alkylation with a suitable methylating reagent such as TMS-diazomethane. transformation is typically carried out at low temperatures, e.g., 0°C, and after the addition, the reaction is allowed to warm to ambient temperatures, e.g., about 25°C (Scheme 2). This methyl ester is then converted to the N-hydroxyamide derivative of this invention by treatment with aqueous hydroxylamine (e.g., aqueous 50% hydroxylamine) in a polar organic solvent such as dioxane and the like. The reaction is carried out at ambient temperature for about 2 to 6 hours.

[00106] Synthesis of compounds of Formula II is further illustrated by Scheme F below.

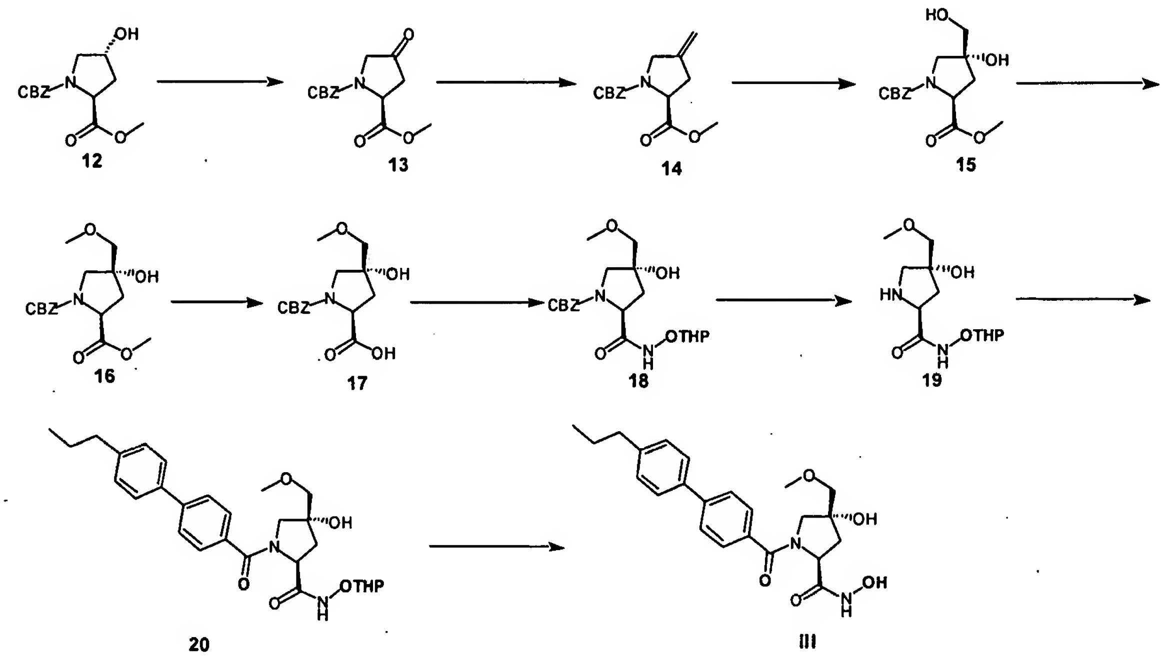


VI

[00107] Scheme F: Reagents and conditons: (a) 1N NaOH; (b) $(COCl)_2$, DMF (cat), DCM, 0 °C; (c) THF; (d) 1. $TMSCHN_2$, MeOH, 0 °C to rt, 2. NH_2OH, MeOH

Compound of Formula III can be prepared as illustrated in Schemes 4 and 5.

Scheme 4



[00108] The conventional oxidation of the hydroxyl group of compound 12 (e.g.,Swern oxidation, pyridinium dichromate or dess-Martin oxidation conditions) provides N-protected 4-oxoproline methyl ester, compound 13 (Scheme 4). Reaction of compound 13 with dibromomethane, Zn and bis(cyclopentadienyl)zirconium dichloride in organic solvent , for example, THF provided the alkene derivative 14. Hydroxylation under Sharpless condition furnished di-hydroxy compound (15)

[00109] Compound 15 is selectively O-methylated with an alkylating agent in the presence of a base to provide the alkylated product 16 (Scheme 4).. Suitable methylating agents include trimethyloxonium tetrafluoroborate and the like. The alkylation is conducted in an inert organic solvent such as, for example, N,N-dimethylformamide, acetonitrile, dichloromethane, and N-methylpyridone. Suitable bases include, 2,6-di-tert-butyl-4-methylpyridine, triethylamine and the like. The reaction is typically conducted at room temperature for about 2 to about 16 hours.

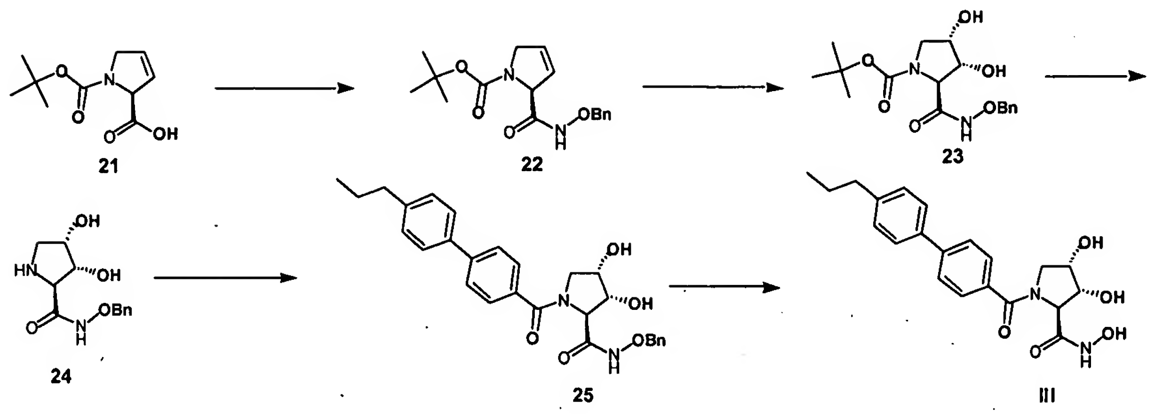
[00110] The methyl ester 17 is then treated with aqueous inorganic base in polar solvent to hydrolyze the methyl ester protecting group and then coupled with an O-protected hydroxyl amine. Suitable base include lithium hydroxide, sodium hydroxide and suitable organic solvents include methanol, tetrahydrofuran and dioxane. The acid is coupled with the O-protected hydroxylamine using a coupling reagent such as HATU in an organic base in an inert organic solvent. Suitable organic bases include DIEA, TEA, pyridine, and N-methyl morpholine, and suitable inert organic solvents include N,N-dimethylformamide, acetonitrile, dichloromethane, and alike.

[00111] The O-protected amide is then hydrogenated to remove the N-protecting group to provide a amine 19 (Scheme 4). The hydrogenation is carried out in a polar organic solvent such as methanol. The reduction is carried out in the presence of a palladium (II) catalyst under hydrogen atmosphere. The reduction may conveniently be carried out at ambient temperatures in about 2 minutes to 6 hours.

[00112] The amine (19) is then condensed with an optionally substituted aromatic acid , preferably in an inert organic solvent, in the presence of a coupling reagent and an organic base to provide an amide 20 (Scheme 4). This reaction can be performed with any number of known coupling reagents, such as HATU, HOBT, carbodiimides, DPPA, and the like. Suitable organic bases include DIEA, TEA, pyridine, N-methyl morpholine, and the like. Suitable inert organic solvents which can be used include, for example, N,N-dimethylformamide, acetonitrile, dichloromethane, and the like. The reaction is continued until completion, which typically occurs in from about 2 to 12 hours.

[00113] The amide 20 is then converted to the N-hydroxyamide derivative of Formula (III) by treatment with acid in a organic solvent such as dichloroethane, methylene chloride and the like. The reaction is carried out at ambient temperature for about 2 to 6 hours.

Scheme 5



[00114] The Boc-protected compound 21 is coupled with O-benzyl hydroxylaminehydrochloride under reactive conditions, preferably in an inert organic solvent, in the presence of a coupling reagent and an organic base to provide a benzyloxyamide 22 (Scheme 5). This reaction can be performed with any number of known coupling reagents, such as HATU, HOBT, carbodiimides, DPPA, and the like. Suitable organic bases include DIEA, TEA, pyridine, N-methyl morpholine, and the like. Suitable inert organic solvents which can be used include, for example, N,N-dimethylformamide, acetonitrile, dichloromethane, and the like. This reaction is typically conducted at temperatures in the range of about 0°C to 25°C. The reaction is continued until completion, which typically occurs in from about 2 to 12 hours.

[00115] The hydroxylated compound 23 can be prepared by methods well known in the art (Scheme 5). Suitable hydroxylating agents for alkene to the alcohol include OsO_4 and 4-methylmorpholine-N-oxide in t-butanol and Sharpless reagents. The reaction is generally carried out from about 12 to 24 hours.

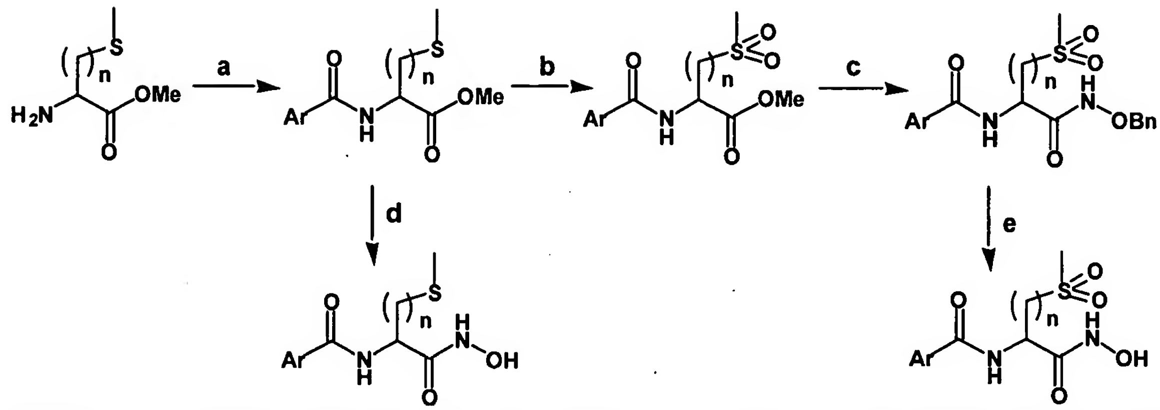
[00116] The benzyloxyamide is then reacted with an acid to remove the t-butoxycarbonyl protecting group (Scheme 5).Removal of the protecting group may be carried out with acids, such as a trifluoroacetic acid (TFA), hydrochloric acid, *p*-toluenesulfonic acid, and the like, in an inert organic solvent such as dichloromethane, dioxane, THF, and the like. The removal is

typically conducted at low temperatures, e.g., 0°C, and then gradually allowed to warm to room temperature to provide the benzyloxyamide acid salt.

[00117] Benzyloxyamide acid salt is then condensed with an optionally substituted biphenyl acid under reactive conditions, preferably in an inert organic solvent, in the presence of a coupling reagent and an organic base to provide an amide (25). This reaction can be performed with any number of known coupling reagents, such as HATU, HOBT, carbodiimides, DPPA, and the like. Suitable organic bases include DIEA, TEA, pyridine, N-methylmorpholine, and the like. Suitable inert organic solvents which can be used include, for example, N,N-dimethylformamide, acetonitrile, dichloromethane, and the like. This reaction is typically conducted using an excess of benzyloxyamide to benzoic acid at temperatures in the range of about 0°C to about 50°C. The reaction is continued until completion, which typically occurs in from about 2 to 12 hours.

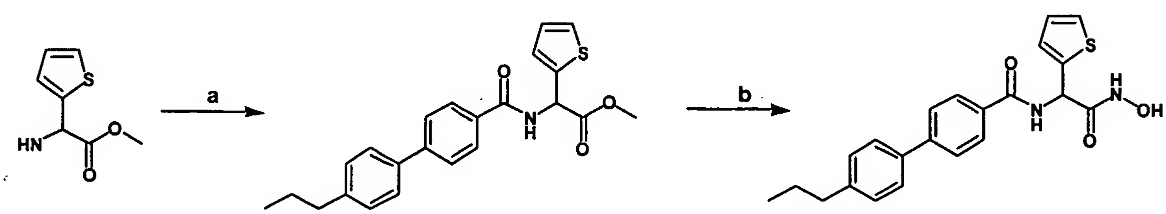
[00118] Compound 25 is then converted to the N-hydroxyamide derivative of Formula (III) by hydrogenation to remove the benzyloxy protecting group (OBn (Scheme 5). Deprotection is carried out in a polar organic solvent such as methanol. The hydrogenation is carried out at in the presence of a palladium (II) catalyst or palladium on carbon under hydrogen atmosphere. The hydrogenation conveniently may be carried at ambient temperatures in about 30 minutes to 2 hours.

[00119] General synthesis of N-aroyl 2-(methylthio)alkyl glycine hydroxamate derivatives is illustrated in Scheme G below.

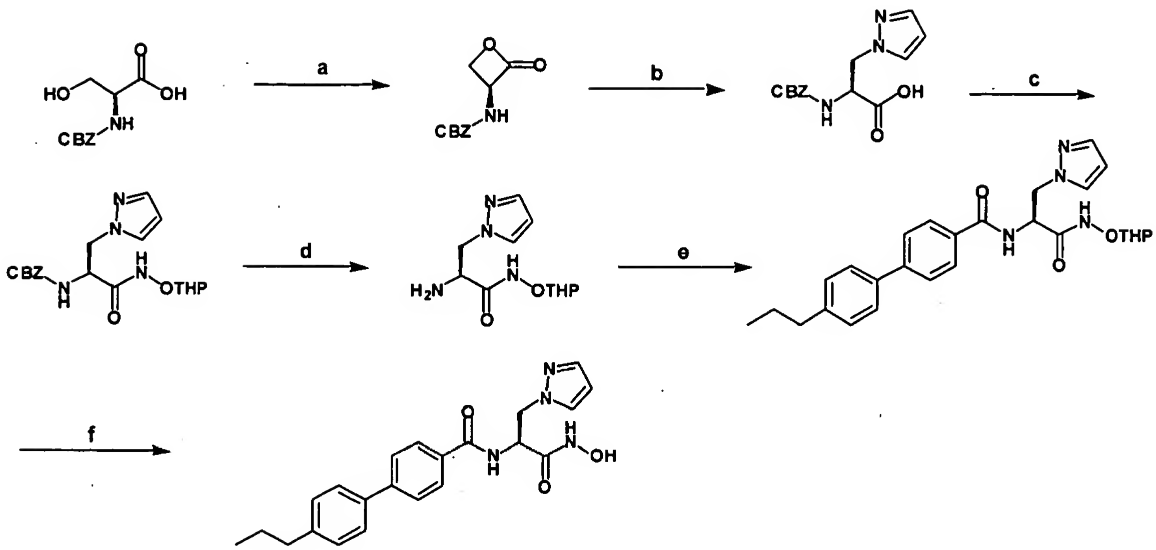


[00120] Scheme **G:** Reagents and conditions. (a) Coupling (ArCOOH, HATU, DIEA, DMF). (b) Oxidation (MCPBA, DCM). (c) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene). (d) Hydroxamate formation (NH_2OH.HCl, NaOMe, MeOH). (e) Hydroxamate formation (10% $Pd(OH)_2$, EtOH).

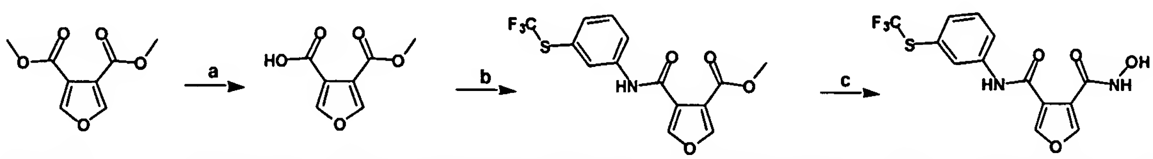
[00121] Synthesis of heterocyclic amino acid derivatives of this invention is illustrated in Schemes H-J below.



[00122] Scheme **H** : Reagents and conditions. (a) 4-(4-n-propylphenyl)benzoic acid, HATU, DIEA, DMF, rt, 18 h; (b) hydroxylamine hydrochloride, MeOH, NaOMe, rt, 2 h.



[00123] Scheme I: Reagents and conditions. (a) DIAD, Ph3P, THF, -78 °C, 3h 50 min; (b) pyrazole, ACN, 55°C, 24 h; (c) HATU, DIEA, DMF, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, rt, 18 h; (d) 10% Pd/C, EtOH, H_2, rt, 8 h; (e) 4-(4-n-propylphenyl)benzoic acid, HATU, DIEA, DMF, rt, 18 h (f) TFA, DCM, rt, 2 h.



[00124] Scheme J: Reagents and conditions. (a) NaOH water, MeOH, 4°C, 18 h; (b) HATU, DIEA, DMF, 3-(trifluoromethylthio) aniline, rt, 18 h; (c) hydroxylamine hydrochloride, MeOH, NaOMe, rt, 2 h.

Examples

[00125] In the discussion above and in the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

7-methylMTL	=	1-methylsulfanyl-7-*deoxy*-7-methyllincosamine
Ac	=	acetyl
ACN	=	acetonitrile
Alloc	=	allyloxycarbonyl protecting group
apt	=	apparent triplet
Aq	=	aqueous
atm	=	atmospheres
Bn	=	benzyl
Boc	=	*tert*-butoxycarbonyl protecting group
Boc_2O	=	di-*tert*-butyl dicarbonate
br s	=	broad singlet
BSTFA	=	*N,O*-bis(trimethylsilyl)trifluoroacetamide
^{13}C NMR	=	^{13}carbon nuclear magnetic resonance
Cbz	=	benzyloxycarbonyl protecting group
$CDCl_3$	=	deuterated chloroform
CD_3OD	=	deuterated methanol
CD_3SOCD_3	=	deuterated dimethylsulfoxide
CH_2Br_2	=	dibromomethane
$(CH_3)_3OBF_4$	=	trimethyloxonium tetrafluoroborate
Cp_2ZrCl_2	=	bis(cyclopentadienyl)zirconium dichloride
cfu	=	colony forming units
D_2O	=	deuterated water
d	=	doublet
DAST	=	dimethylaminosulfurtrifluoride
dd	=	doublet of doublets
dddd	=	doublet of doublets of doublet of doublets
DIBALH	=	diisobutylaluminum hydride
dt	=	doublet of triplets
DCE	=	dicholoroethane
DCM	=	dichloromethane
DIAD	=	diisopropyl azodicarboxylate
DIEA	=	diisopropyethylamine
DMAP	=	dimethylaminopyridine
DMF	=	dimethylformamide
DMS	=	dimethyl sulfide
DMSO	=	dimethyl sulfoxide
DPPA	=	diphenylphosphoryl azide
ED_{50}	=	dose therapeutically effective in 50% of the population
EDCI	=	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride

eq.	=	equivalents
ESMS	=	electrospray mass spectrometry
Et	=	ethyl
EtOAc	=	ethyl acetate
Et_2O	=	diethyl ether
Et_2N	=	triethylamine
g	=	grams
h	=	hours
H_2	=	hydrogen
HATU	=	*O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	=	*O*-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	=	1-hydroxybenzotriazole hydrate
^1H NMR	=	Hydrogen nuclear magnetic resonance spectroscopy
HPLC	=	high pressure liquid chromatography
Hz	=	hertz
IC_{50}	=	concentration of the test compound which achieves a half-maximal inhibition of symptoms
J	=	coupling constant in hertz
L	=	liters
LD_{50}	=	dose lethal to 50% of the population
LiHMDS	=	lithium hexamethyldisilazide
LiOH	=	lithium hydroxide
m	=	multiplet
M	=	molar
MCPBA	=	3-chloroperoxybenzoic acid
Me	=	methyl
MeCN	=	acetonitrile
MeOH	=	methanol
mg	=	milligrams
MHB	=	Mueller Hinton broth
MHz	=	megahertz
MIC	=	minimum inhibitory concentration
min	=	minutes
mL	=	milliliters
mm	=	millimeter
mmHg	=	millimeters mercury
mmol	=	millimol
Ms	=	mesyl
MS(ESPOS)	=	mass spectrometry by positive mode electrospray ionization
MS(ESNEG)	=	mass spectrometry by negative mode electrospray ionization
MTBU	=	7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene
MTL	=	1-methylsulfanyllincosamine (methyl 6-amino-6,8-dideoxy-1-thio-*erythro*-α-D-galacto-octopyranoside)

N	=	normal
NaOMe	=	sodium methoxide
NBS	=	N-bromosuccinimide
NMR	=	nuclear magnetic resonance, δ in ppm
NMM	=	4-methylmorpholine
NMO	=	4-methylmorpholin N-oxide
OBz	=	benzoate ester protecting group
O*t*Bu	=	*tert*-butoxy
ONPG	=	2-Nitrophenyl ß-D-galactopyranoside
OsO_4	=	osmium tetraoxide
*i*PrOAc	=	*iso*-propyl acetate
PDC	=	pyridinium dichromate
Pd/C	=	palladium on carbon
pg	=	picograms
Ph	=	phenyl
Ph_3P	=	triphenylphosphine
Pro	=	L-proline
psi	=	pounds per square inch
q	=	quartet
q.v.	=	quantitative
R_f	=	retention factor
rt	=	room temperature
s	=	singlet
sat.	=	saturated
t	=	triplet
TBABS	=	tetrabutylammonium bisulfate
TBAF	=	tetrabutylammonium fluoride
t-BuOH	=	tert-butyl alcohol
TCI	=	TCI America
TEA	=	triethylamine
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
TMS	=	trimethylsilyl
$TMSCHN_2$	=	(trimethylsilyl)diazomethane
TMEDA	=	trimethylethylenediamine
TPAP	=	tetrapropylammonium perruthenate
Ts	=	tosyl
μg	=	micrograms
μL	=	microliters
μM	=	micromolar
v/v	=	volume by volume

General Methods

[00126] **Method A:** To a stirred solution of the carboxylic acid # (20.3 mmol) in tetrahydrofuran (75 ml) was added di-*tert*-butyl dicarbonate (2.5 eq.., 50.8 mmol) followed by the addition of sodium bicarbonate (6 eq.., 122 mmol) in water (75 ml). The carboxylic acids are commercially available from vendors like Aldrich, Acros, Anaspec, CNH technologies, etc. The addition is typically carried out at low temperatures, e.g. 0°C, after which the reaction was brought to rt and let to stir for 16 h. The reaction was concentrated to remove all solvent, diluted with excess water and extracted with ether. The aqueous layer was acidified with 6N HCl and extracted with DCM (2x) and once with n-butanol. All organic extracts were combined, concentrated, and co-evaporated with toluene. The residue was then dried under high vacuum to give the desired Boc-protected carboxylic acid

[00127] **Method B:** The Boc-protected acid # (7.35 mmol, 1 eq.) was taken into THF-MeOH (1:1) and the reaction cooled to 0°C. 2M $TMSCHN_2$ in ether (7.35 ml, 2 eq.) was added with stirring in one portion, and the reaction stirred at 0°C for 2 h. The reaction was monitored by TLC (eluent: 4:1 hexanes-ethyl acetate). Solvent was removed under vacuum. The residue was purified by SiO_2 column chromatography (gradient 20%-40% ethyl acetate in hexanes) to provide the desired methyl ester

[00128] **Method C:** DIAD (1.5 eq) was added to a mixture of the *trans*-hydroxyproline methyl ester (1.0 eq.), benzoic acid (1.5 eq.) and triphenylphosphine (1.5 eq.) in THF at 0°C. The reaction was slowly warmed to rt and stirred for an additional 16 h. Solvents were removed under vacuum, and the residue triturated with ether at 0°C to remove triphenylphosphine oxide. Upon filtration, the filtrate was concentrated and subjected to column chromatography (SiO_2, gradient 25%-35% ethyl acetate/hexanes) to give the desired O-benzoyl protected intermediate

[00129] **Method D:** The *cis*-O-benzoyl protected methyl ester was taken into MeOH and 0.5M sodium methoxide was added with stirring at 0°C. The reaction was stirred at rt for 2 h. It was then neutralized with Amberlite H+ resin, filtered, concentrated under high pressure and purified by SiO_2 column chromatography (gradient 10-20% acetone in DCM) to give the corresponding *cis*-3-hydroxyproline methyl ester

[00130] **Method E:** DIAD (23.88 mmol, 1.3 eq.) was added dropwise with stirring to a solution of *cis*-3-hydroxyproline methyl ester # (18.36 mmol, 1 eq.) and triphenylphosphine (22.9 mmol, 1.25 eq.) in THF (100 mL) at 0°C. Then a solution of diphenylphosphoryl azide (22.9 mmol, 1.25 eq.) in THF (20 ml) was added. The reaction was slowly warmed to rt and stirred for 16 h. The solvent was then removed under vacuum, and the residue triturated with cold ether to remove triphenylphosphine oxide. Upon filtration, the filtrate was concentrated and subjected to column chromatography (SiO_2, gradient 15%-20% ethyl acetate/hexanes) to give the desired *trans*-3-azido-proline compound

[00131] **Method F:** The Boc-protected methyl ester was taken into excess 4M HCl/dioxane (25 ml) and the reaction stirred at rt for 4 h. It was then concentrated, and the residue triturated with ether to precipitate the desired hydrochloric acid salt #. This salt was dried under high vacuum.

[00132] **Method G:** Carboxylic acid (0.91 mmol), DMF (20 mL), and DIEA (0.64 ml, 3.67 mmol) are combined and stirred at rt. Amine (1.19 mmol) and HATU (451 mg, 1.19 mmol) are added to the stirring mixture. The combined mixture is stirred for 18 h. Ethyl acetate (100 ml) is added. The diluted mixture is washed consecutively with 10% citric acid solution, brine, saturated sodium bicarbonate solution, and again with brine. The ethyl acetate layer is dried over sodium sulfate and concentrated *in vacuo*. The crude product is used in the next reaction without further purification. In cases where purification was required, the compounds purified by column chromatography (SiO_2, gradient 30-40% ethyl acetate/hexanes).

[00133] **Method H:** Methyl ester (0.76 mmol), hydroxylamine hydrochloride (524 mg, 7.54 mmol), and MeOH are stirred at rt. Sodium methoxide (98%, 499 mg, 9.05 mmol) is added, and the reaction is monitored by HPLC. If the reaction is not completed within 2 h, an additional charge of sodium methoxide (98%, 499 mg, 9.05 mmol) is added and the reaction is monitored again by HPLC. The crude mixture is concentrated, dissolved in DMSO, and purified by preparative-HPLC.

[00134] **Method I:** 2M Trimethylaluminium in toluene (4 eq.) was slowly added to a suspension of the O-benzylhydroxylamine hydrochloride (4 eq.) in toluene at 0°C under nitrogen. The reaction was brought to rt slowly and stirred for 1 h. This mixture was then added to a solution of the methyl ester # (1 eq.) in toluene at rt. The combined mixture was heated at 54°C for 1-2 h, and the reaction was monitored by TLC (7:3 hexanes/ethyl acetate). Solvent was removed under vacuum, and the residue taken into excess ethyl acetate, washed with 10% citric acid (2x) and brine once. The organic extract was dried over sodium sulfate, filtered, concentrated and purified by column chromatography (SiO_2, gradient 0-10% acetone/DCM) to provide the protected hydroxamate intermediate.

[00135] **Method J:** To a solution of the protected hydroxamate # (1.37 mmol) in ethanol (25 ml) under a nitrogen atmosphere, 10%/wt of 10% Pd/C (70 mg) was added and the reaction evacuated and stabilized to a hydrogen atmosphere. The reaction was stirred for 12 h, filtered through a pad of Celite and the filtrate concentrated to provide the desired final inhibitor.

[00136] **Method K:** To a solution of the methyl ester # (8.93 mmol) in ethanol (50 ml), with small amounts of MeOH to dissolve the compound, under a nitrogen atmosphere, 10% Pd/C (350-400 mg; ca. 10% weight of the substrate #) was added and the reaction evacuated and stabilized to a hydrogen atmosphere. The reaction is stirred for 2-3 h, filtered through a pad of Celite and the filtrate concentrated to provide the desired free amine compound .

[00137] **Method L:** To a cold solution of the 3-aminoproline intermediate # (0.137 mmol, 1 eq.) in pyridine, methanesulfonyl chloride (1 eq.) was added slowly, and the reaction was stirred at 0°C for 30 min. It was slowly brought to rt and stirred for an additional 16 h. The reaction was concentrated, and the residue was taken into excess ethyl acetate. The organic mixture was washed with 10% citric acid and brine. The combined organic extracts were dried over sodium sulfate, filtered, concentrated and purified by column chromatography (SiO_2, gradient 15-25% acetone/DCM) to provide the desired sulfonamide.

[00138] **Method M:** A 5:1 mixture of formic acid and acetic anhydride was heated at 60°C for 1-1.5 h. The mixture was cooled and added to the 3-aminoproline intermediate #, and the mixture stirred for 8-24 h. The reaction was monitored by HPLC. It was concentrated under vacuum, co-evaporated with toluene and DCM, and the residue purified by column chromatography (SiO_2, gradient 0-30% acetone/DCM, then 2.5%-5% MeOH/DCM) to provide the N-formyl compound .

[00139] **Method N:** A solution of the N-formyl intermediate (1.78 mmol, 1 eq.) in tetrahydrofuran was cooled to 0°C. Commercially available borane-methylsulfide complex (3.36 mmol, 2 eq.) was added drop-wise and the mixture stirred at rt for 5 h. It was then quenched with MeOH (15 ml) and stirred at rt for an additional 16 h. 2M HCl/MeOH was added, and the reaction mixture refluxed for 3 h. The reaction was concentrated, and excess DCM was added. Under stirring conditions at 0°C sodium bicarbonate was slowly added till the ph of the reaction was ~8. The organic layer was separated and the aqueous layer thoroughly washed with DCM. The organic extracts were combined, dried over sodium sulfate, filtered, concentrated and purified by column chromatography (SiO_2, 0-20% acetone/DCM, then 2.5%-5% MeOH/DCM) to provide the desired N-methylated intermediate.

[00140] **Method O:** To a solution of the 3-hydroxyproline methyl ester # in DCM at –78°C, DAST (4 eq.) was added dropwise with stirring. The reaction was slowly warmed to rt. It was stirred at rt for 16 h, then diluted with more DCM and washed with cold sat. sodium bicarbonate, dried over sodium sulfate, filtered, concentrated and purified by column chromatography (SiO_2, 20-30% ethyl acetate/hexanes) to provide the desired 3-fluoroproline intermediate .

[00141] **Method P:** To a solution of the protected hydroxamate # (0.65 mmol) in ethanol (25 ml) under a nitrogen atmosphere, 10%/wt of 10% $Pd(OH)_2/C$ was added, and the reaction vessel was charged with hydrogen. The reaction was stirred for 8 h, filtered through a pad of Celite, and the filtrate concentrated to provide the desired final inhibitor .

[00142] **Method Q:** To a solution of the 3-hydroxyproline compound (4 g, 1 eq.) in DMF (50 ml), was added methyl iodide (5.3 ml, 5 eq.) and silver oxide (11.3 g, 3 eq.), and the reaction was stirred for 16 h. The reaction mixture was then diluted with ethyl acetate and filtered through Celite. The filtrate was washed with brine, 10% sodium thiosulfate, sat. sodium bicarbonate, and dried over sodium sulfate. The organic extracts were concentrated and purified by column chromatography (SiO_2, gradient 20-40% ethyl acetate/hexanes) to provide the desired intermediate .

[00143] **Method R:** HPLC analysis conditions –are as follows. YMC-Pak Pro C18, S-3 μm, 120A, 50 x 4.6 mm I.D. Column; gradient eluent 0% - 90% MeCN in water (both solvents containing 0.1% TFA) over 8.5 min, 1.5 mL/min.

[00144] **Method S:** The methyl ester # (1 eq.) was taken into DCM and the reaction was cooled to –40°C. MCPBA (2 eq.) in DCM was added very slowly. The temperature of the reaction was maintained below –5°C for 2 h during which the reaction was monitored for completion by TLC in hexanes/ethyl acetate (2:3). The reaction provided both the sulfone and the sulfoxide intermediates. Upon completion, excess DCM was added to the reaction mixture and washed with cold sat. sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated. The residue obtained was purified by column chromatography (SiO_2, hexanes/ethyl acetate and acetone/DCM) to afford the desired oxidized intermediate(s) # and/or .

[00145] **Method T:** The methyl ester was taken into a mixture of THF-MeOH (1:1 v/v). 50% aq. hydroxylamine /water followed by catalytic amounts of potassium cyanide was then added to the reaction mixture. The reaction was allowed to stir at rt for 16 h. Solvents were removed under vacuum, and the residue was taken into water and the compound extracted into the ethyl acetate layer. The organic layer was dried over sodium sulfate, filtered, concentrated and purified by preparative HPLC to give the final inhibitor.

[00146] **Method U:** A solution of anhydrous DMSO (22.7 mL, 320 mmol) in anhydrous DCM (600 mL) is stirred at -78°C under nitrogen. Oxalyl chloride (13.9 mL, 159 mmol) is slowly added at a rate to maintain a temperature below -65°C. The mixture is stirred for an additional 15 min, and alcohol (126 mmol) in DCM (125 mL) is added. After an additional 30 min of stirring, triethylamine (85.0 mL, 610 mmol) is added. The mixture is stirred while slowly warming to rt (ca. 80 min). This is diluted with DCM and washed with 10% citric acid solution. The DCM layer is separated, washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product is purified by column chromatography (SiO_2, 30%-50% ethyl acetate in hexanes).

[00147] **Method V:** Ketone (1.08 mmol), Zn (566 mg, 8.66 mmol), bis(cyclopentadienyl)zirconium dichloride (380 mg, 1.30 mmol), and THF (2 mL are combined and stirred at rt under nitrogen. Dibromomethane (0.17 mL, 2.44 mmol) is slowly added to the mixture. The internal temperature slowly increased to ca. 30 °C. The reaction mixture is stirred for 3 h, and is quenched with water. The solution is extracted twice with ether. The organic layers are combined, dried over sodium sulfate, and concentrated under vacuum. The crude material is purified by column chromatography (SiO_2, 30% ethyl acetate in hexanes).

[00148] **Method W:** Alkene (0.362 mmol), 4-methylmorpholine N-oxide (47 mg, 0.401 mmol), 2.5% OsO_4 in t-BuOH (0.46 mL, 0.037 mmol), acetone (4 mL), and water (0.25 mL) were combined and stirred at rt for 18 h. The reaction mixture was concentrated under vacuum. The crude product was purified by column chromatography (10 % MeOH in DCM).

[00149] **Method X:** Alcohol (1.62 mmol), 2,6-di-tert-butyl-4-methylpyridine (664 mg, 3.23 mmole), and anhydrous DCM (10 mL) are combined and stirred at 4 °C. Trimethyloxonium tetrafluoroborate (239 mg, 1.62 mmole) is added to the reaction mixture, and the combination mixture is stirred for 1 h at 4 °C. The mixture is warmed to room tempertature and allowed to stir for an additional 4 h. The mixture is diluted with DCM and washed with saturated, aqueous $NaHCO_3$ solution. The organic layer is dried over sodium sulfate, and

concentrated under vacuum. The crude material is purified by column chromatography (3% MeOH in DCM).

[00150] **Method Y:** Methyl ester (0.921 mmol), lithium hydroxide monohydrate (50.8 mg, 1.21 mmol), water (10 mL), and MeOH (10 mL) are combined and stirred at reflux for 1 hour. The mixture is cooled, and acidified with 10% HCl to pH=1. The aqueous mixture is extracted with EtOAc, dried over sodium sulfate, and concentrated under vacuum. The crude product is used in the next reaction without further purification.

[00151] **Method Z:** An appropriate N-benzyl or N-benzyl carbamate (0.311 mmol), 10% Pd on carbon (33 mg, 0.031 mmol), and EtOH (5 mL) are combined and stirred under H_2 at rt for 8 h. The reaction mixture is concentrated *in vacuo*. The crude material is used in the next reaction without further purification, unless specifically stated.

[00152] **Method AA:** Tetrahydropyranyl protected alcohol or BOC protected amine (0.580 mmol) and 20% TFA in DCM (50 ml) is stirred at rt for 2 h. The reaction is concentrated *in vacuo* and used without further purification unless specifically stated.

[00153] **Method BB**: Methyl ester (54.63 mmol), NaOH (54.74 mmol), water (300 mL), and MeOH (300 mL) are combined and stirred at 4°C for 18 h. The aqueous layer is washed with ether. The extracted aqueous layer is acidified to pH 1 with 1N HCl. The acidic solution is extracted with ethyl acetate. The ethyl acetate layer is dried over sodium sulfate, concentrated *in vacuo*, and used in the next step without further purification.

[00154] **Method CC**: Alkene (1.14 mmol), OsO_4 (4% in water, 0.70 mL, 0.11 mmol), *tert*-butyl alcohol (2 mL), acetone (15 mL), and 4-methylmorpholine *N*-oxide (147 mg, 1.25 mmol) are combined and stirred at rt for 18 h. The reaction mixture is concentrated *in vacuo*, and purified by column chromatography (SiO_2, 0 - 20% MeOH in DCM). Two separate diastereomeric epoxides are obtained.

[00155] **Method DD**: Epoxide (0.74 mmol), sodium azide (1.45 g, 22.26 mmol), DMF (10 mL), and water (2 mL) are combined and stirred at 80°C for 18 h. Water is added to the reaction mixture, and the mixture is extracted with ethyl acetate. The ethyl acetate layer is washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo*. The compound was used in the next reaction without further purification.

[00156] **Method EE**: 4-(4-n-Propylphenyl)benzoic acid (130mg, 0.53 mmol), DCM (8 ml), DMF (1 drop), and oxalyl chloride (0.09 ml, 1.03 mmol) are combined and stirred at rt for 1 h. The reaction mixture is concentrated *in vacuo*, and the residue is redissolved in DCM (8 mL). The amine (0.47 mmol) is dissolved in pyridine and combined with the DCM mixture. The combined mixture is stirred at rt for 18 h, and diluted with ethyl acetate. The ethyl acetate solution is washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The compound was used in the next reaction without further purification.

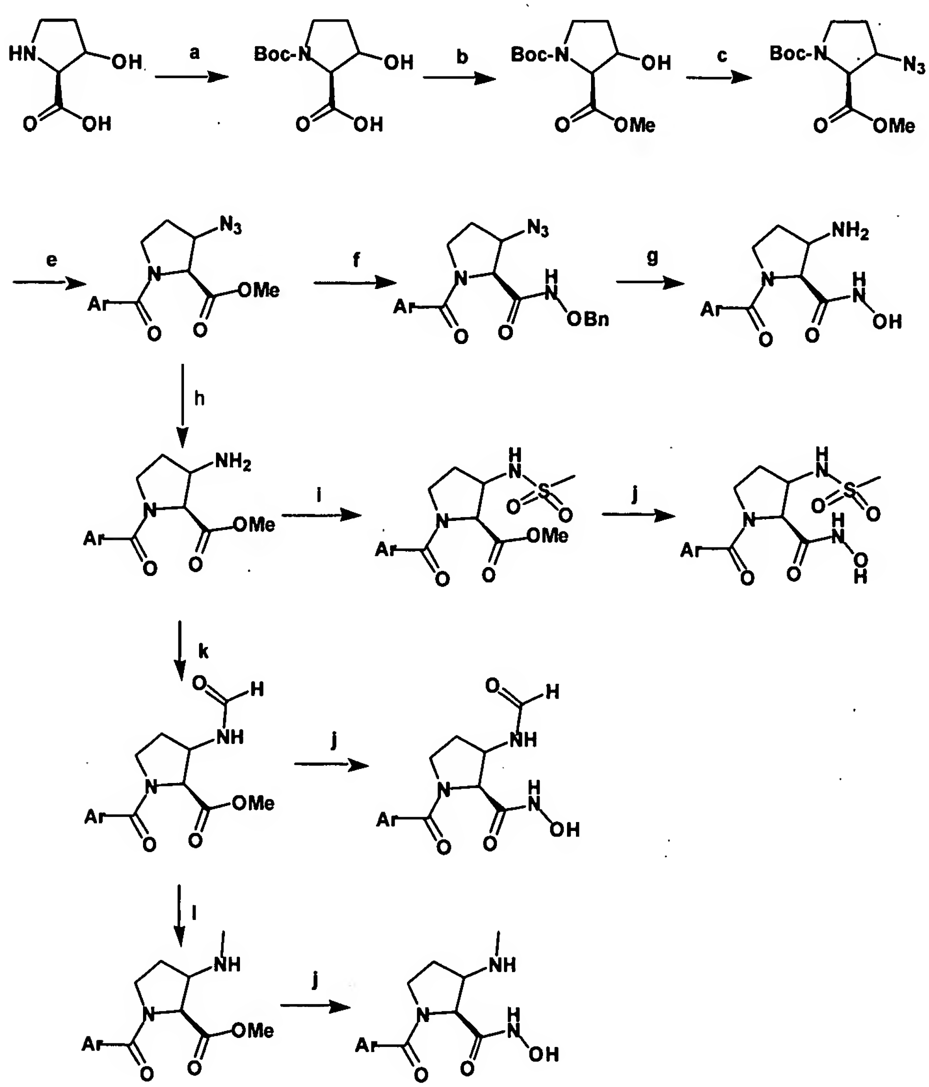
[00157] **Method FF:** To a stirred solution or suspension of the acid (1 mmol, 1 eq) in DCM (3-5 mL) was added few drops of DMF. The resulting solution was cooled to 0 °C in ice bath followed by addition of 2M $(COCl)_2$ in toluene (1 mL, 2 eq.). This mixture was stirred at 0 °C for 3 h, and solvents were removed under vacuum to yield relatively pure acid chloride. The residue was suspended in anhydrous THF (2-3 mL), and resulting suspension was cooled to 0 °C. To this suspension was added amino acid (0.5 mmol) dissolved in 1N NaOH solution (1-2 mL). The resulting mixture was stirred at rt for 16 h followed by addition of 1N HCl to pH 3. The resulting mixture was extracted with EtOAc (3x10 mL). The combined organic phase was washed with sat. aq. $NaHCO_3$, brine, and dried over Na_2SO_4. Solvent was removed under vacuum to yield a mixture of the product along with starting acid as indicated by TLC and MS analysis.

[00158] The above mixture was dissolved in MeOH (3-5 mL) followed by cooling to 0 °C. To this mixture was added 2M solution of $TMSCHN_2$ in diethyl ether (4 ml, 8 eq.). This mixture was stirred at 0 °C for 10 min, and then for 20 min at rt. The yellow solution was concentrated under reduced pressure and purified by column chromatography to yield pure methyl ester.

[00159] **Method GG**: To a stirred solution of above ester (1 mmol) in MeOH (3-5 mL) was

added a 50% aq. solution of NH_2OH(1-2 mL). This mixture was stirred at rt for 30 min to 16 h, at which time the reaction was complete as detected by HPLC. The reaction was concentrated under reduced pressure and the resulting residue was suspended in MeOH/water to prepare a clear solution. This solution was then purified via preparative HPLC to yield the pure product.

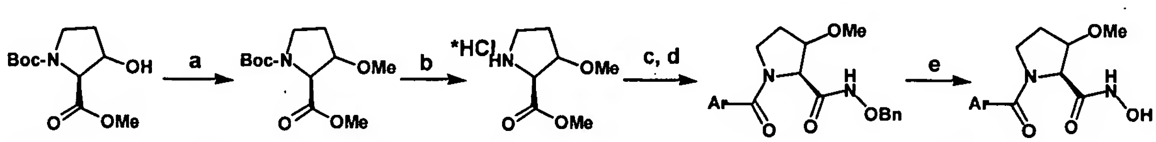
General synthesis of 1-Aroyl 3-Amino Prolyl Hydroxamate Derivatives



14 15

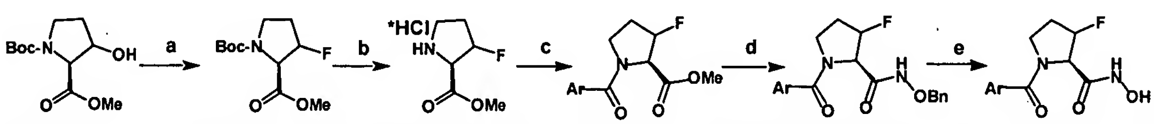
[00160] **Scheme A.** Reagents and conditions. (a) Protection (Boc_2O, base); (b) Methyl ester formation ($TMSCHN_2$, MeOH); (c) Azide substitution (DPPA, DIAD, Ph_3P); (d) Deprotection (4M HCl/Dioxane); (e) Coupling (ArCOOH, HATU, DIEA, DMF); (f) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (g) Hydroxamate formation (10% Pd/C, H_2, EtOH); (h) Reduction (10% Pd/C, H_2, EtOH). (i) Sulfonamidation (CH_3SO_2Cl, Pyridine); (j) Hydroxamate formation (NH_2OH.HCl, NaOMe, MeOH). (k) N-Formylation (HCOOH, Ac_2O); (l) Reduction ($BH_3.(CH_3)_2S$, THF, MeOH).

General synthesis of 1-Aroyl 3-Alkoxyprolyl Hydroxamate Derivatives



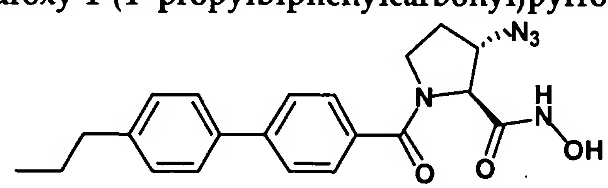
[00161] **Scheme B:** Reagents and conditions. (a) O-Alkylation ($TMSCHN_2$, MeOH); (b) Deprotection (4M HCl/Dioxane); (c) Coupling (ArCOOH, HATU, DIEA, DMF); (d) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (e) Hydroxamate formation (10% $Pd(OH)_2$/C, EtOH).

General synthesis of 1-Aroyl 3-Fluoroprolyl Hydroxamate Derivatives



[00162] **Scheme C:** Reagents and conditions. (a) Fluroine substitution (DAST, DCM); (b) Deprotection (4M HCl/Dioxane); (c) Coupling (ArCOOH, HATU, DIEA, DMF); (d) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (e) Hydroxamate formation (10% $Pd(OH)_2$/C, EtOH).

Example 1
(2*S*,3*S*)-3-Azido-*N*-hydroxy-1-(4′-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



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[00163] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-Hydroxypyrrolidine-2-carboxylic acid following Method A_(yield = 91%)._The resulting product was used without purification._ ^{1}H NMR (DMSO-d_6): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52 (d, 9H). HPLC: Rt = 3.868 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00164] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid following Method B (quantitative yield). ^{1}H NMR ($CDCl_3$): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

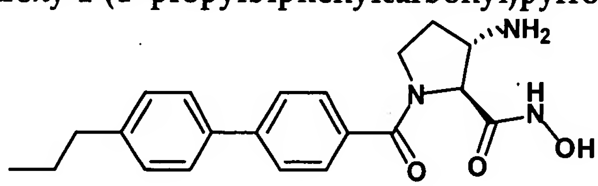
[00165] Step 3: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Methods C, D and E (overall yield = 90%). ^{1}H NMR (DMSO-d_6): 4.65 – 4.61 (m, 1H), 4.26 – 4.25 (d, J = 2.73 Hz, 1H), 3.89 – 3.87 (d, J = 7.41 Hz, 3H), 3.83 – 3.52 (m, 2H), 2.32 – 2.12 (m, 2H), 1.47 – 1.42 (d, J = 20.6 Hz, 9H). HPLC: Rt = 5.94 following Method R. ES-MS: calcd. for $C_{11}H_{18}N_4O_4$ (270.29); found: 271.4 [M+H].

[00166] Step 4: (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.9 – 4.84 (m, 1H), 4.53 – 4.51 (d, J = 5.77 Hz, 1H), 3.75 (s, 3H), 3.5 – 3.45 (t, J = 7.42 Hz. 2H), 2.5 – 2.43 (dd, J = 7.42 & 7.14 Hz, 1H), 2.13 – 2.06 (m, 1H). ES-MS: calcd. for $C_6H_{10}N_4O_2$ (170.29); found: 171.2

[00167] Step 5: (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 75%). ^{1}H NMR (DMSO-d_6): 7.95 – 7.92 (d, J = 8.24 Hz, 2H), 7.83 – 7.81 (d, J = 7.97 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 4.74 – 4.71 (m, 1H), 4.63 – 4.62 (d, J = 3.3 Hz, 1H), 3.92 (s, 3H), 3.89 – 3.5 (m, 2H), 2.69 – 2.68 (t, J = 1.65 & 1.92 Hz, 2H), 2.44 – 2.37 (m, 1H), 2.23 – 2.18 (m, 1H), 1.85 – 1.78 (m, 2H), 1.13 – 1.08 (t, J = 3.42 Hz, 3H). HPLC: Rt = 6.36 following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (392.45); found: 393.1 [M+H].

[00168] Step 6: (2*S*,3*S*)-3-azido-*N*-hydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method H (yield = 25%). ^{1}H NMR (DMSO-d_6): 10.96 (bs, 1H), 9.06 (bs, 1H), 7.81 – 7.61 (m, 6H), 7.31 – 7.29 (d, J = 7.97 Hz, 2H), 6.53 (bs, 1H), 4.36 – 4.1 (m, 1H), 3.67 – 3.57(m, 2H), 2.62 – 2.57 (t, J = 7.42 Hz, 2H), 2.26 (bs, 1H), 1.98 (bs, 1H), 1.65 – 1.58 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.36 following Method R. ES-MS: calcd. for $C_{21}H_{23}N_5O_3$ (393.45); found: 416.2 [M+Na].

Example 2
(2*S*,3*S*)-3-Azido-*N*-hydroxy-1-(4′-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00169] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-Hydroxypyrrolidine-2-carboxylic acid following Method A (yield = 91%). The resulting product was used without purification. ^{1}H NMR (DMSO-d_6): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52 (d, 9H). HPLC: Rt = 3.868 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00170] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid following Method B (quantitative yield). ^{1}H NMR ($CDCl_3$): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

[00171] Step 3: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Methods C, D and E (overall yield = 90%). ^{1}H NMR (DMSO-d_6): 4.65 – 4.61 (m, 1H), 4.26 – 4.25 (d, J = 2.73 Hz, 1H), 3.89 – 3.87 (d, J = 7.41 Hz, 3H), 3.83 – 3.52 (m, 2H), 2.32 – 2.12 (m, 2H), 1.47 – 1.42 (d, J = 20.6 Hz, 9H). HPLC: Rt = 5.94 min following Method R. ES-MS: calcd. for $C_{11}H_{18}N_4O_4$ (270.29); found: 271.4 [M+H].

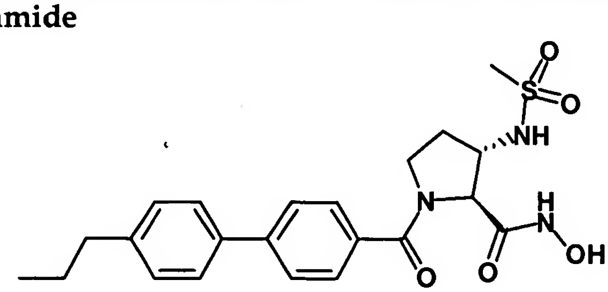
[00172] Step 4: (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate following Method F (quantitiative yield). ^{1}H NMR (DMSO-d_6): 4.9 – 4.84 (m, 1H), 4.53 – 4.51 (d, J = 5.77 Hz, 1H), 3.75 (s, 3H), 3.5 – 3.45 (t, J = 7.42 Hz. 2H), 2.5 – 2.43 (dd, J = 7.42 & 7.14 Hz, 1H), 2.13 – 2.06 (m, 1H). ES-MS: calcd. for $C_6H_{10}N_4O_2$ (170.29); found: 171.2

[00173] Step 5: (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 75%). ^{1}H NMR (DMSO-d_6): 7.95 – 7.92 (d, J = 8.24 Hz, 2H), 7.83 – 7.81 (d, J = 7.97 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 4.74 – 4.71 (m, 1H), 4.63 – 4.62 (d, J = 3.3 Hz, 1H), 3.92 (s, 3H), 3.89 – 3.5 (m, 2H), 2.69 – 2.68 (t, J = 1.65 & 1.92 Hz, 2H), 2.44 – 2.37 (m, 1H), 2.23 – 2.18 (m, 1H), 1.85 – 1.78 (m, 2H), 1.13 – 1.08 (t, J = 3.42 Hz, 3H). HPLC: Rt = 7.19 min following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (392.45); found: 393.1 [M+H].

[00174] Step 6: (2*S*,3*S*)-3-azido-*N*-(benzyloxy)-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method I (yield = 89%). ^{1}H NMR (DMSO-d_6): 11.79 (bs, 1H), 7.95 – 7.76 (m, 5H), 7.63 – 7.48 (m, 8H), 5.02 (bs, 1H), 4.51 (bs, 2H), 4.44 – 4.28 (m, 1H), 3.92 (s, 3H), 3.86 – 3.77 (m, 2H), 2.82 – 2.77 (t, J = 7.14 & 7.97 Hz, 2H), 2.4 (bs, 1H), 2.16 (bs, 1H), 1.88 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 7.19 min following Method R. ES-MS: calcd. for $C_{28}H_{29}N_5O_3$ (483.56); found: 484.1 [M+H].

[00175] Step 7: (2*S*,3*S*)-3-amino-*N*-hydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-3-azido-*N*-(benzyloxy)-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide following Method J (yield = 30 - 40%). ^{1}H NMR (DMSO-d_6): 11.1 (bs, 1H), 9.312 (bs, 1H), 8.52 (bs, 2H), 7.96 – 7.82 (m, 6H), 7.52 – 7.5 (d, J = 8.24 Hz, 2H), 4.79 (bs, 1H), 4.05 (bs, 1H), 3.91 – 3.85 (m, 2H), 2.82 – 2.77 (t, J = 7.69 & 7.42 Hz, 2H), 2.48 (m, 1H), 2.23 (bs, 1H), 1.85 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 5.12 min following Method R. ES-MS: calcd. for $C_{21}H_{25}N_3O_3$ (367.45); found: 368.3 [M+H].

Example 3
(2*S*,3*S*)-*N*-Hydroxy-3-(methylsulfonamido)-1-(4′-propylbiphenylcarbonyl) pyrrolidine-2-carboxamide



[00176] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-Hydroxypyrrolidine-2-carboxylic acid following Method A (yield = 91%). The resulting product was used without purification. ^{1}H NMR (DMSO-d_6): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52

(d, 9H). HPLC: Rt = 3.868 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00177] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid following Method B (quantitative yield). ^{1}H NMR ($CDCl_3$): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

[00178] Step 3: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate was prepare from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Methods C, D and E (overall yield = 90%). ^{1}H NMR (DMSO-d_6): 4.65 – 4.61 (m, 1H), 4.26 – 4.25 (d, J = 2.73 Hz, 1H), 3.89 – 3.87 (d, J = 7.41 Hz, 3H), 3.83 – 3.52 (m, 2H), 2.32 – 2.12 (m, 2H), 1.47 – 1.42 (d, J = 20.6 Hz, 9H). HPLC: Rt = 5.94 min following Method R. ES-MS: calcd. for $C_{11}H_{18}N_4O_4$ (270.29); found: 271.4 [M+H].

[00179] Step 4: (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.9 – 4.84 (m, 1H), 4.53 – 4.51 (d, J = 5.77 Hz, 1H), 3.75 (s, 3H), 3.5 – 3.45 (t, J = 7.42 Hz. 2H), 2.5 – 2.43 (dd, J = 7.42 & 7.14 Hz, 1H), 2.13 – 2.06 (m, 1H). ES-MS: calcd. for $C_6H_{10}N_4O_2$ (170.29); found: 171.2

[00180] Step 5: (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 75%). ^{1}H NMR (DMSO-d_6): 7.95 – 7.92 (d, J = 8.24 Hz, 2H), 7.83 – 7.81 (d, J = 7.97 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 4.74 – 4.71 (m, 1H), 4.63 – 4.62 (d, J = 3.3 Hz, 1H), 3.92 (s, 3H), 3.89 – 3.5 (m, 2H), 2.69 – 2.68 (t, J = 1.65 & 1.92 Hz, 2H), 2.44 – 2.37 (m, 1H), 2.23 – 2.18 (m, 1H), 1.85 – 1.78 (m, 2H), 1.13 –

1.08 (t, J = 3.42 Hz, 3H). HPLC: Rt = 7.19 min following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (392.45); found: 393.1 [M+H].

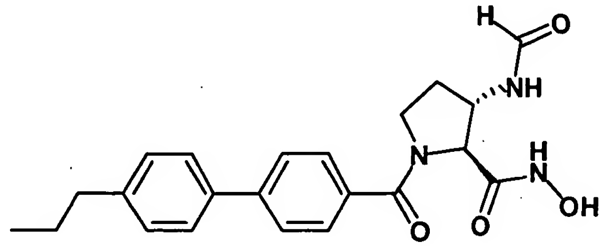
[00181] Step 6: (2*S*,3*S*)-methyl-3-amino-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method K (quantitative yield). ^{1}H NMR (DMSO-d_6): 7.74 – 7.60 (m, 7H), 7.38 – 7.29 (m, 3H), 4.15 – 4.13(d, J = 4.12 Hz, 1H), 3.72 – 3.46 (m, 3 H), 3.68 – 3.67 (d, J = 1.37 Hz, 3H), 2.62 – 2.57 (t, J = 7.42 Hz, 2H), 2.1 – 1.97 (m, 2H), 1.7 – 1.58 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.48 min following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (366); found: 367.2 [M+H].

[00182] Step 7: (2*S*,3*S*)-methyl-3-(methylsulfonamido)-1-(4'-propylbiphenylcarbonyl)pyrrolidine

-2-carboxylate was prepared from (2*S*,3*S*)-methyl-3-amino-1-(4'propylbiphenylcarbonyl) pyrrolidine-2-carboxylate following Method L (yield = 67%). ^{1}H NMR (DMSO-d_6): 7.82 – 7.60 (m, 6H), 7.38 – 7.36 (d, J = 8.24 Hz,, 1H), 7.32 – 7.29 (d, J = 7.97 Hz, 2H), 4.37 – 4.35 (d, J = 4.7 Hz, 1H), 4.08 – 4.01 (t, J = 6.04 & 7.69 Hz, 1H), 4.01 – 3.62 (m, 2H), 3.69 (bs, 3H), 2.99 (bs, 3H), 2.5 – 2.49 (t, J = 1.92 & 1.65 Hz, 2H), 2.2 – 2.16 (dd, J = 6.04 – 6.59 Hz, 1H), 1.98 – 1.87 (m, 2H), 1.68 – 1.5 (m, 2H), 0.93 – 0.84 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.47 min following Method R. ES-MS: calcd. for $C_{23}H_{28}N_2O_5S$ (444.54); found: 445.2 [M+H].

[00183] Step 8: (2*S*,3*S*)-*N*-hydroxy-3-(methylsulfonamido)-1-(4'-propylbiphenylcarbonyl) pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-methyl-3-(methylsulfonamido)-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method H (yield = 40%). ^{1}H NMR (DMSO-d_6): 11.06 (bs, 1H), 7.94 – 7.80 (m, 7H), 7.62 – 7.6 (d, J = 7.69 Hz,, 1H), 7.50 – 7.48 (d, J = 8.24 Hz, 2H), 4.45 – 4.44 (d, J = 3.84 Hz, 1H), 4.13 – 4.11 (d, J = 4.67 Hz, 1H), 3.83 – 3.78 (t, J = 6.59 & 6.86 Hz, 2H), 3.17 (bs, 3H), 2.81 – 2.76 (t, J = 7.42 & 7.69 Hz, 2H), 2.45 – 2.39 (m, 1H), 2.06– 1.98 (m, 1H), 1.87 – 1.74 (m, 2H), 1.12 – 1.07 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.47 min following Method R. ES-MS: calcd. for $C_{22}H_{27}N_3O_5S$ (445.54); found: 446.3 [M+H].

Example 4
(2*S*,3*S*)-3-Formamido-*N*-hydroxy-1-(4′-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00184] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-hydroxypyrrolidine-2-carboxylic acid following Method A (yield = 91%). The resulting product was used without purification. ^{1}H NMR (DMSO-d_6): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52 (d, 9H). HPLC: Rt = 3.868 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00185] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid following Method B (quantitative yield). ^{1}H NMR ($CDCl_3$): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

[00186] Step 3: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Methods C, D and E (overall yield = 90%). ^{1}H NMR (DMSO-d_6): 4.65 – 4.61 (m, 1H), 4.26 – 4.25 (d, J = 2.73 Hz, 1H), 3.89 – 3.87 (d, J = 7.41 Hz, 3H), 3.83 – 3.52 (m, 2H), 2.32 – 2.12 (m, 2H), 1.47 – 1.42 (d, J = 20.6 Hz, 9H). HPLC: Rt = 5.94 min following Method R. ES-MS: calcd. for $C_{11}H_{18}N_4O_4$ (270.29); found: 271.4 [M+H].

[00187] Step 4: (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d$_6$): 4.9 – 4.84 (m, 1H), 4.53 – 4.51 (d, J = 5.77 Hz, 1H), 3.75 (s, 3H), 3.5 – 3.45 (t, J = 7.42 Hz. 2H), 2.5 – 2.43 (dd, J = 7.42 & 7.14 Hz, 1H), 2.13 – 2.06 (m, 1H). ES-MS: calcd. for $C_6H_{10}N_4O_2$ (170.29); found: 171.2

[00188] Step 5: (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 75%). ^{1}H NMR (DMSO-d$_6$): 7.95 – 7.92 (d, J = 8.24 Hz, 2H), 7.83 – 7.81 (d, J = 7.97 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 4.74 – 4.71 (m, 1H), 4.63 – 4.62 (d, J = 3.3 Hz, 1H), 3.92 (s, 3H), 3.89 – 3.5 (m, 2H), 2.69 – 2.68 (t, J = 1.65 & 1.92 Hz, 2H), 2.44 – 2.37 (m, 1H), 2.23 – 2.18 (m, 1H), 1.85 – 1.78 (m, 2H), 1.13 – 1.08 (t, J = 3.42 Hz, 3H). HPLC: Rt = 7.19 min following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (392.45); found: 393.1 [M+H].

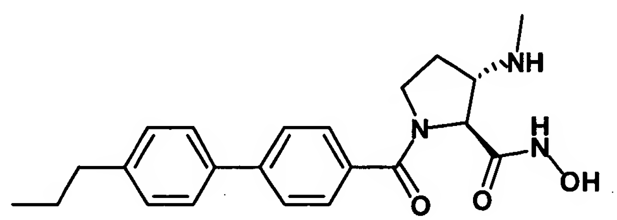
[00189] Step 6: (2*S*,3*S*)-methyl-3-amino-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method K (quantitative yield). ^{1}H NMR (DMSO-d$_6$): 7.74 – 7.60 (m, 7H), 7.38 – 7.29 (m, 3H), 4.15 – 4.13 (d, J = 4.12 Hz, 1H), 3.72 – 3.46 (m, 3 H), 3.68 – 3.67 (d, J = 1.37 Hz, 3H), 2.62 – 2.57 (t, J = 7.42 Hz, 2H), 2.1 – 1.97 (m, 2H), 1.7 – 1.58 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.48 min following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (366); found: 367.2 [M+H].

[00190] Step 7: (2*S*,3*S*)-methyl-3-formamido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl-3-amino-1-(4'-propylbiphenylcarbonyl) pyrrolidine-2-carboxylate following Method M (yield = 80%). ^{1}H NMR (DMSO-d$_6$): 8.82 - 8.8 (d, J = 7.42 Hz, 2H), 8.27 (bs, 1H), 7.96 – 7.93 (d, J = 7.69 Hz, 2H), 7.84 – 7.81 (d, J = 8.24 Hz, 4H), 7.51 – 7.49 (d, J = 7.42 Hz, 2H), 4.7 – 4.63 (dd, J = 6.59 & 6.32 Hz, 1H), 4.48 – 4.46 (d, J = 5.22 Hz, 1H), 3.863 –3.86 (d, J = 1.098 Hz, 3H), 3.88 – 3.67 (m, 2H), 2.82 – 2.77 (t, J = 7.97 & 7.42 Hz, 2H), 2.34 – 2.28 (dd, J = 6.87 & 6.59 Hz, 1H), 2.1 – 2.03 (dd, J = 6.87 & 5.77 Hz, 1H),

1.88 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 6.25 min following Method R. ES-MS: calcd. for $C_{23}H_{26}N_2O_4$ (394.16); found: 417.3 [M+Na].

[00191] Step 8: (2*S*,3*S*)-3-formamido-*N*-hydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-methyl-3-formamido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method H (yield = 33%). ^{1}H NMR (DMSO-d$_6$): 10.97 (bs, 1H), 8.76 - 8.74 (d, J = 7.14 Hz, 1H), 8.22 (bs, 1H), 7.94 – 7.81 (m, 6H), 7.61 – 7.58 (d, J = 7.42 Hz, 1H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 4.56 (bs, 1H), 4.42 (bs, 1H), 3.82 –3.77 (m, 2H), 2.36 – 2.32 (m, 1H), 2.81 – 2.76 (t, J = 7.69 Hz, 2H), 2.1 – 2.03 (dd, J = 6.87 & 5.77 Hz, 1H), 1.96 – 1.94 (m, 1H), 1.87 – 1.77 (m, 2H), 1.12 – 1.07 (t, J = 7.42 Hz, 3H). HPLC: Rt = 5.64 min following Method R. ES-MS: calcd. for $C_{22}H_{25}N_3O_4$ (395.46); found: 396.3 [M+H].

Example 5
(2*S*,3*S*)-Methyl-3-(methylamino)-1-(4′-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00192] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-Hydroxypyrrolidine-2-carboxylic acid following Method A (yield = 91%). The resulting product was used without purification. ^{1}H NMR (DMSO-d$_6$): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52 (d, 9H). HPLC: Rt = 3.868 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00193] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid

NB1:662111.3

following Method B (quantitative yield). ^{1}H NMR ($CDCl_3$): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

[00194] Step 3: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Methods C, D and E (overall yield = 90%). ^{1}H NMR (DMSO-d_6): 4.65 – 4.61 (m, 1H), 4.26 – 4.25 (d, J = 2.73 Hz, 1H), 3.89 – 3.87 (d, J = 7.41 Hz, 3H), 3.83 – 3.52 (m, 2H), 2.32 – 2.12 (m, 2H), 1.47 – 1.42 (d, J = 20.6 Hz, 9H). HPLC: Rt = 5.94 min following Method R. ES-MS: calcd. for $C_{11}H_{18}N_4O_4$ (270.29); found: 271.4 [M+H].

[00195] Step 4: (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.9 – 4.84 (m, 1H), 4.53 – 4.51 (d, J = 5.77 Hz, 1H), 3.75 (s, 3H), 3.5 – 3.45 (t, J = 7.42 Hz. 2H), 2.5 – 2.43 (dd, J = 7.42 & 7.14 Hz, 1H), 2.13 – 2.06 (m, 1H). ES-MS: calcd. for $C_6H_{10}N_4O_2$ (170.29); found: 171.2

[00196] Step 5: (2*S*,3*S*)-methyl 3-azido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azidopyrrolidine-2-carboxylate and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 75%). ^{1}H NMR (DMSO-d_6): 7.95 – 7.92 (d, J = 8.24 Hz, 2H), 7.83 – 7.81 (d, J = 7.97 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 4.74 – 4.71 (m, 1H), 4.63 – 4.62 (d, J = 3.3 Hz, 1H), 3.92 (s, 3H), 3.89 – 3.5 (m, 2H), 2.69 – 2.68 (t, J = 1.65 & 1.92 Hz, 2H), 2.44 – 2.37 (m, 1H), 2.23 – 2.18 (m, 1H), 1.85 – 1.78 (m, 2H), 1.13 – 1.08 (t, J = 3.42 Hz, 3H). HPLC: Rt = 7.19 min following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (392.45); found: 393.1 [M+H].

[00197] Step 6: (2*S*,3*S*)-methyl-3-amino-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-azido-1-(4'-

propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method K (quantitative yield). ^{1}H NMR (DMSO-d_6): 7.74 – 7.60 (m, 7H), 7.38 – 7.29 (m, 3H), 4.15 – 4.13 (d, J = 4.12 Hz, 1H), 3.72 – 3.46 (m, 3 H), 3.68 – 3.67 (d, J = 1.37 Hz, 3H), 2.62 – 2.57 (t, J = 7.42 Hz, 2H), 2.1 – 1.97 (m, 2H), 1.7 – 1.58 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.48 min following Method R. ES-MS: calcd. for $C_{22}H_{24}N_4O_3$ (366); found: 367.2 [M+H].

[00198] Step 7: (2*S*,3*S*)-methyl-3-formamido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl-3-amino-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method M (yield = 80%). ^{1}H NMR (DMSO-d_6): 8.82 - 8.8 (d, J = 7.42 Hz, 2H), 8.27 (bs, 1H), 7.96 – 7.93 (d, J = 7.69 Hz, 2H), 7.84 – 7.81 (d, J = 8.24 Hz, 4H), 7.51 – 7.49 (d, J = 7.42 Hz, 2H), 4.7 – 4.63 (dd, J = 6.59 & 6.32 Hz, 1H), 4.48 – 4.46 (d, J = 5.22 Hz, 1H), 3.863 –3.86 (d, J = 1.098 Hz, 3H), 3.88 – 3.67 (m, 2H), 2.82 – 2.77 (t, J = 7.97 & 7.42 Hz, 2H), 2.34 – 2.28 (dd, J = 6.87 & 6.59 Hz, 1H), 2.1 – 2.03 (dd, J = 6.87 & 5.77 Hz, 1H), 1.88 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 6.25 min following Method R.

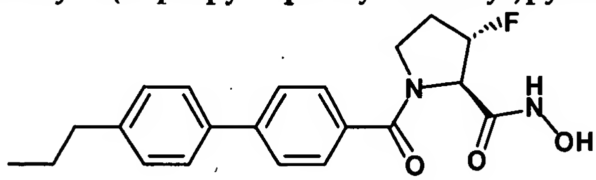
ES-MS: calcd. for $C_{23}H_{26}N_2O_4$ (394.16); found: 417.3 [M+Na].

[00199] Step 8: (2*S*,3*S*)-methyl-3-(methylamino)-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl-3-formamido-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method N (yield = 59%). ^{1}H NMR (DMSO-d_6): 7.74 – 7.71 (d, J = 8.24 Hz, 2H), 7.63 – 7.58 (dd, J = 6.59 & 6.87 Hz, 4H), 7.31 – 7.28 (d, J = 7.97 Hz, 2H), 5.78 – 5.74 (m, 1H), 4.32 – 4.31 (d, J = 3.02 Hz, 1H), 3.72 – 3.58 (m, 1H), 3.68 (bs, 3H), 3.57 – 3.5 (m, 1H), 3.2 – 3.15 (t, J = 6.04 & 5.22 Hz, 1H), 2.62 – 2.56 (t, J = 7.42 & 7.69 Hz, 2H), 2.05 – 1.97 (m, 1H), 1.81 – 1.77 (m, 1H), 1.68 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.55 min following Method R. ES-MS: calcd. for $C_{23}H_{28}N_2O_3$ (380.21); found: 381.2 [M+H].

[00200] Step 9: (2*S*,3*S*)-*N*-hydroxy-3-(methylamino)-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-methyl-3-(methylamino)-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method H

(yield = 20%). ^{1}H NMR (DMSO-d_6): 11.19(bs, 1H), 9.36 – 9.25 (m, 2H), 7.95 – 7.81 (m, 5H), 7.51 – 7.48 (d, J = 8.24 Hz, 2H), 4.88 (bs, 1H), 4.0 – 3.85 (m, 3H), 2.88 (s, 3H), 2.81 – 2.76 (t, J = 7.14 & 7.97 Hz, 2H), 2.5 – 2.34 (m, 2H), 1.87 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.187 min following Method R. ES-MS: calcd. for $C_{22}H_{27}N_3O_3$ (381.476); found: 382.3 [M+H].

Example 6
(2*S*,3*S*)-3-Fluoro-*N*-hydroxy-1-(4′-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00201] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-Hydroxypyrrolidine-2-carboxylic acid following Method A (yield = 91%). The resulting product was used without purification. ^{1}H NMR (DMSO-d_6): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52 (d, 9H). HPLC: Rt = 3.868 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00202] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid following Method B (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

[00203] Step 3: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-azidopyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Methods C, D and E (overall yield = 90%). ^{1}H NMR (DMSO-d_6): 4.65 – 4.61 (m, 1H), 4.26 – 4.25 (d, J = 2.73 Hz, 1H), 3.89 – 3.87 (d, J = 7.41 Hz, 3H), 3.83 – 3.52 (m, 2H), 2.32 – 2.12 (m,

2H), 1.47 – 1.42 (d, J = 20.6 Hz, 9H). HPLC: Rt = 5.94 min following Method R. ES-MS: calcd. for $C_{11}H_{18}N_4O_4$ (270.29); found: 271.4 [M+H].

[00204] Step 4: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-fluoropyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*R*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Method O (yield = 46%). ^{1}H NMR (DMSO-d_6): 5.74 – 5.23 (m, 1H), 4.4 – 4.3 (dd, J = 22.52 & 23.08 Hz, 1H), 3.69 (s, 3H), 3.66 – 3.31 (m, 2H), 2.15 – 1.93 (m, 2H), 1.4 – 1.33 (d, J = 21.42 Hz, 9H). HPLC: Rt = 5 min following Method R. ES-MS: calcd. for $C_{11}H_{18}FNO_4$ (247.26)

[00205] Step 5: (2*S*,3*S*)-methyl 3-fluoropyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-fluoropyrrolidine-1,2-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 5.86 – 5.68 (dd, J = 1.65 & 2.74 Hz, 1H), 4.93 – 4.85 (d, J = 22.8 Hz, 1H), 3.98 (s, 3H), 3.68 – 3.49 (m, 2H), 2.49 – 2.3 (m, 2H). ES-MS: calcd. for $C_6H_{10}FNO_2$ (147.15); found 148.2 [M+H].

[00206] Step 6: (2*S*,3*S*)-methyl 3-fluoro-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-fluoropyrrolidine-2-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 78%). ^{1}H NMR (DMSO-d_6): 7.75 – 7.72 (d, J = 8.24 Hz, 2H), 7.66 – 7.61 (d, J = 6.32 & 5.77 Hz, 4H), 7.31 – 7.29 (d, J = 7.97 Hz, 2H), 5.52 – 5.34 (d, J = 52.47 Hz, 1H), 4.74 – 4.66 (d, J = 22.53 Hz, 1H), 3.72 (s, 3H), 3.83 – 3.34 (m, 2H), 2.62 – 2.56 (t, J = 7.69 Hz, 2H), 2.24 – 2.06 (m, 2H), 1.67 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H).

HPLC: Rt = 7.10 min following Method R. ES-MS: calcd. for $C_{22}H_{24}FNO_3$ (369.17); found: 370 [M+H].

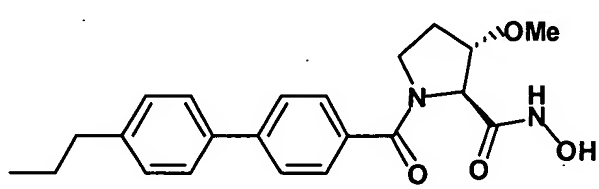
[00207] Step 7: (2*S*,3*S*)-*N*-(benzyloxy)-3-fluoro-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-methyl 3-fluoro-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method I (yield = 60%). ^{1}H NMR (DMSO-d_6): 11.82 (bs, 1H), 7.95 – 7.77 (m, 6H), 7.66 – 7.49 (m, 7H), 5.45 – 5.28 (d, J =

52.74 Hz, 1H), 5.03 (bs, 1H), 4.81 – 4.74 (m, 2H), 3.9 – 3.89 (d, J = 5.77 Hz, 2H), 2.82 – 2.77 (t, J = 7.69 & 7.42 Hz, 2H), 2.41 – 2.32 (m, 2H), 1.85 – 1.78 (m, 2H), 1.13 – 1.09 (t, J = 5.77 & 7.14 Hz, 3H). HPLC: Rt = 7.06 min following Method R. ES-MS: calcd. for $C_{28}H_{29}FN_2O_3$ (460.54)

[00208] Step 8: (2*S*,3*S*)-3-fluoro-*N*-hydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-*N*-(benzyloxy)-3-fluoro-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide following Method P (yield = 25%). ^{1}H NMR (DMSO-d_6): 11.2 (bs, 1H), 7.94 – 7.81 (m, 6H), 7.6 – 7.57 (d, J = 6.87 Hz, 1H), 7.51 – 7.48 (d, J = 8.24 Hz, 2H), 5.49 – 5.32 (d, J = 52.2 Hz, 1H), 4.87 – 4.8 (d, J = 22.53 Hz, 1H), 3.93 – 3.79 (m, 2H), 2.82 – 2.77 (t, J = 7.42 & 7.69 Hz, 2H), 2.43 – 2.34 (m, 2H), 1.87 – 1.80 (m, 2H), 1.13 – 1.09 (t, J = 7.42 Hz, 3H). HPLC: Rt = 6.09 min following Method R. ES-MS: calcd. for $C_{21}H_{23}FN_2O_3$ (370.42); found 371 [M+H].

Example 7

(2*S*,3*S*)-*N*-Hydroxy-3-methoxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00209] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-Hydroxypyrrolidine-2-carboxylic acid following Method A (yield = 91%). The resulting product was used without purification. ^{1}H NMR (DMSO-d_6): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52 (d, 9H). HPLC: Rt = 3.87 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00210] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid

following Method B (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

[00211] Step 3: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-methoxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Method Q (yield = 90%). ^{1}H NMR (DMSO-d_6): 4.17 - 4.1 (d, J = 2.2 Hz, 1H), 3.94 – 3.91 (d, J = 10.16 Hz, 1H), 3.67 – 3.65 (dd, J = 1.65 Hz, 3H), 3.47 – 3.41 (m, 1H), 3.7 – 3.26 (d, J = 1.65 Hz, 3H), 1.93 – 1.90 (dd, J = 4.67 & 3.57 Hz, 2H), 1.38 – 1.31 (dd, J = 1.37 Hz, 9H). HPLC: Rt = 4.93 min following Method R. ES-MS: calcd. for $C_{12}H_{21}NO_5$ (259.3); found: 282.1 [M+Na].

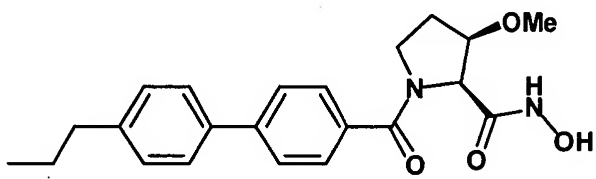
[00212] Step 4: (2*S*,3*S*)-methyl 3-methoxypyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-methoxypyrrolidine-1,2-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.4 - 4.38 (d, J = 2.2 Hz, 1H), 4.24 – 4.2 (dd, J = 4.94 & 3.57 Hz, 1H), 3.77 (s, 3H), 3.38 – 3.3 (m, 1H), 3.3 (s, 3H), 3.3 – 3.16 (m, 2H), 2.03 – 1.97 (dd, J = 4.67 & 3.57 Hz, 2H), ES-MS: calcd. for $C_7H_{13}NO_3$ (159.18); found: 160.4 [M+H].

[00213] Step 5: (2S,3S)-methyl 3-methoxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*S*)-methyl 3-methoxypyrrolidine-2-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (quantitative yield). ^{1}H NMR (DMSO-d_6): 7.73 – 7.71 (d, J = 8.24 Hz, 2H), 7.63 – 7.6 (dd, J = 3.85 & 4.12 Hz, 4H), 7.31 – 7.28 (d, J = 7.97 Hz, 2H), 4.5 (s, 1H), 4.02 – 4.0 (d, J = 4.4 Hz, 1H), 3.68 – 3.62 (m, 2H), 3.33 – 3.32 (d, J = 2.2 Hz, 3H), 2.61 – 2.56 (t, J = 7.42 & 7.69 Hz, 2H), 2.06 – 1.98 (m, 2H), 1.65 – 1.57 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.94 min following Method R. ES-MS: calcd. for $C_{23}H_{27}NO_4$ (381.46); found: 382.3 [M+H].

[00214] Step 6: (2*S*,3*S*)-*N*-hydroxy-3-methoxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*S*)-methyl 3-methoxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method H (yield = 20%).

^{1}H NMR (DMSO-d_6): 11.1 (bs, 1H), 7.92– 7.8 (m, 6H), 7.58 – 7.56 (d, J = 7.97 Hz, 4H), 7.51 – 7.48 (d, J = 8.24Hz, 2H), 4.63 (s, 1H), 4.04 (bs, 1H), 3.86 – 3.67 (m, 2H), 3.5 (bs, 3H), 2.81 – 2.76 (t, J = 7.42 & 7.97 Hz, 2H), 2.31 – 2.17 (m, 2H), 1.87 – 1.78 (m, 2H), 1.13 – 1.08 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.05 min following Method R. ES-MS: calcd. for $C_{22}H_{26}N_2O_4$ (382.46); found: 383.3 [M+H].

Example 8
(2*S*,3*R*)-*N*-Hydroxy-3-methoxy-1-(4′-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00215] Step 1: (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid was prepared from (2*S*,3*S*)-3-Hydroxypyrrolidine-2-carboxylic acid following Method A (yield = 91%). The resulting product was used without purification. ^{1}H NMR (DMSO-d_6): 5.64 – 5.63 (d, 1H), 4.42 (bs, 1H), 4.13 – 4.1 (d, 1H), 3.64 – 3.48 (m, 2H), 2.11 – 1.99 (m, 2H), 1.58 – 1.52 (d, 9H). HPLC: Rt = 3.868 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_5$ (231.25); found: 230.2 [M-H].

[00216] Step 2: (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxypyrrolidine-2-carboxylic acid following Method B (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.44 - 4.42 (m, 2H), 4.3 – 4.2 (d, 1H), 3.75 (s, 3H), 3.68 – 3.56 (m, 2H), 2.18 – 2.08 (m, 1H), 1.94 – 1.75 (m, 1H), 1.47 – 1.41 (d, 9H). HPLC: Rt = 4.45 min following Method R. ES-MS: calcd. for $C_{11}H_{19}N_2O_5$ (245.13); found: 268.3 [M+Na].

[00217] Step 5: (2*S*,3*R*)-1-*tert*-butyl 2-methyl 3-methoxypyrrolidine-1,2-dicarboxylate was prepared from (2*S*,3*S*)-1-*tert*-butyl 2-methyl 3-hydroxypyrrolidine-1,2-dicarboxylate following Methods C ,D and Q (yield = 75%). ^{1}H NMR (DMSO-d_6): 4.17 - 4.1 (d, J = 2.2 Hz, 1H), 3.94 – 3.91 (d, J = 10.16 Hz, 1H), 3.67 – 3.65 (dd, J = 1.65 Hz, 3H), 3.47 – 3.41 (m, 1H), 3.7 – 3.26 (d, J = 1.65 Hz, 3H), 1.93 – 1.90 (dd, J = 4.67 & 3.57 Hz, 2H), 1.38 – 1.31 (dd, J = 1.37 Hz, 9H). HPLC: Rt = 4.93 min following Method R. ES-MS: calcd. for $C_{12}H_{21}NO_5$ (259.3); found: 282.1 [M+Na].

[00218] Step 6: (2*S*,3*R*)-methyl 3-methoxypyrrolidine-2-carboxylate hydrochloride salt was prepared from (2*S*,3*R*)-1-*tert*-butyl 2-methyl 3-methoxypyrrolidine-1,2-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.51 - 4.5 (d, J = 3.85 Hz, 1H), 4.28 – 4.26 (dd, J = 4.12 & 1.65 Hz, 1H), 3.77 – 3.76 (d, J = 1.37 Hz, 3H), 3.27 – 3.24 (m, 2H), 3.23 – 3.22 (d, J = 1.65 Hz, 3H), 2.23 – 2.15 (m, 1H), 2.04 – 1.92 (m, 2H),

ES-MS: calcd. for $C_7H_{13}NO_3$ (159.18); found: 160.4 [M+H].

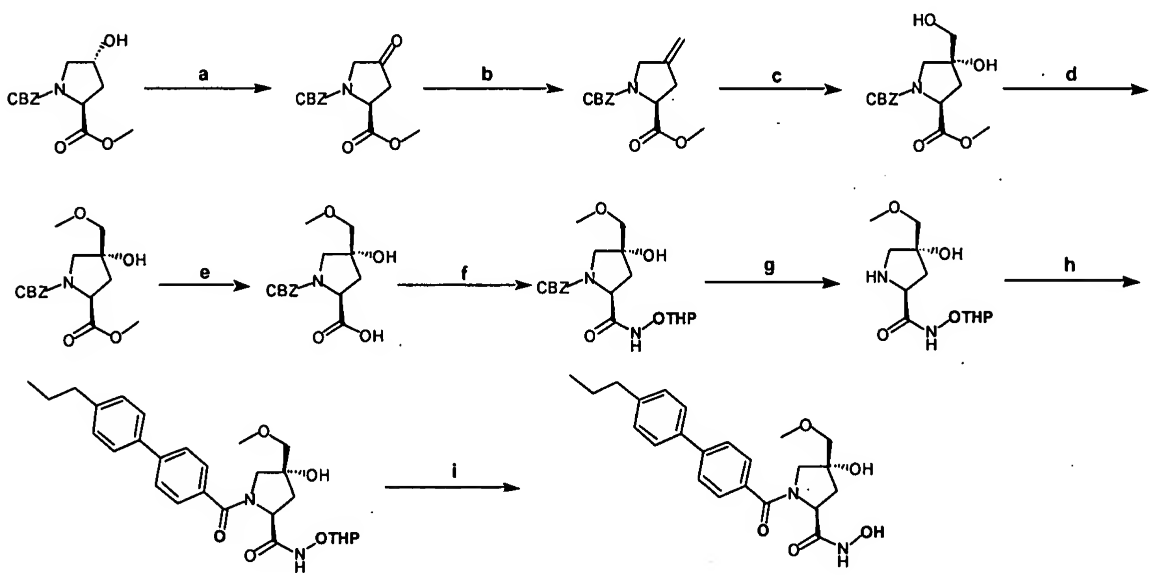
[00219] Step 7: (2*S*,3*R*)-methyl 3-methoxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate was prepared from (2*S*,3*R*)-methyl 3-methoxypyrrolidine-2-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 92%). ^{1}H NMR (DMSO-d_6): 7.74 – 7.72 (d, J = 7.97 Hz, 2H), 7.63 – 7.6 (dd, J = 1.92 & 2.47 Hz, 4H), 7.31 – 7.28 (d, J = 8.24 Hz, 2H), 4.75 – 4.73 (d, J = 6.32 Hz, 1H), 4.25 – 4.22 (t, J = 5.77 & 5.22 Hz, 1H), 3.65 (m, 3H), 3.61 – 3.51 (m, 2H), 3.32 – 3.3 (d, J = 9.34 Hz, 3H), 2.62 – 2.56 (t, J = 7.42 & 7.69 Hz, 2H), 2.06 – 1.94 (m, 2H), 1.65 – 1.57 (m, 2H), 0.93 – 0.88 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 6.91 min following Method R. ES-MS: calcd. for $C_{23}H_{27}NO_4$ (381.46); found: 382.3 [M+H].

[00220] Step 8: (2*S*,3*R*)-*N*-hydroxy-3-methoxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared from (2*S*,3*R*)-methyl 3-methoxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxylate following Method H (yield = 15%). ^{1}H NMR (DMSO-d_6): 10.89 (bs, 1H), 7.72– 7.6 (m, 6H), 7.38 – 7.36 (d, J = 7.97 Hz, 1H), 7.31 – 7.28 (d, J = 8.24 Hz, 2H), 4.43 (s, 1H), 4.09 – 3.83 (m, 1H), 3.63 – 3.43 (m, 2H), 3.33 - 3.2 (m, 3H), 2.61 –

2.5 (m, 2H), 2.11 – 1.95 (m, 2H), 1.67 – 1.55 (m, 2H), 0.93– 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.01 min following Method R. ES-MS: calcd. for $C_{22}H_{26}N_2O_4$ (382.46); found: 383.3 [M+H].

Example 9

Synthesis of (2*S*,4*R*)-*N*,4-Dihydroxy-4-(methoxymethyl)-1-(4'-propylbiphenylcarbonyl) pyrrolidine-2-carboxamide



[00221] Scheme D: Reagents and conditions. (a) DMSO, oxalyl chloride, Et_3N, DCM, -78 °C to rt, 125 min; (b) Cp_2ZrCl_2, CH_2Br_2, Zn, THF, rt to 30 °C, 3 h; (c) OsO_4, NMO, t-BuOH, acetone, water, rt, 18 h; (d) $(CH_3)_3OBF_4$, 2,6-di-tert-butyl-4-methylpyridine, DCM, 4 °C to rt, 5 h; (e) LiOH, MeOH, water, reflux, 1 h; (f) HATU, DIEA, DMF, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, rt, 18 h; (g) 10% Pd/C, EtOH, H_2, rt, 8 h; (h) 4-(4-n-propylphenyl)benzoic acid, oxalyl chloride, DMF, DCM, rt, 1 h; then DCM, pyridine, rt, 18 h; (i) TFA, DCM, rt, 2 h.

[00222] Step 1: (*S*)-1-Benzyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate is prepared from (2*S*,4*R*)-1-benzyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (CBZ-hydroxyproline methyl ester) following Method U (yield = 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.29 (m, 5 H), 5.20-5.09 (m, 2 H), 4.94-4.81 (m, 1 H), 4.07-3.59 (m, 5 H), 3.04-2.87 (m, 1 H), 2.67-2.56 (m, 1 H).

[00223] Step 2: (*S*)-1-Benzyl 2-methyl 4-methylenepyrrolidine-1,2-dicarboxylate is prepared from (*S*)-1-benzyl 2-methyl 4-oxopyrrolidine-1,2-dicarboxylate following Method V (yield = 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.23 (m, 5 H), 5.24-4.97 (m, 4 H), 4.63-4.48 (m, 1 H), 4.22-4.10 (m, 2 H), 3.78-3.56 (m, 3 H), 3.07-2.88 (m, 1 H), 2.72-2.58 (m, 1 H).

[00224] Step 3: (2*S*,4*R*)-1-Benzyl 2-methyl 4-hydroxy-4-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate is prepared from (*S*)-1-benzyl 2-methyl 4-methylenepyrrolidine-1,2-dicarboxylate following Method W (yield = 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5 H), 5.22-4.96 (m, 2 H), 4.61-4.42 (m, 1 H), 3.82-3.44 (m, 7 H), 2.37-1.86 (m, 2 H); ESI(+) calcd. for $C_{15}H_{19}NNaO_6$ (332.11), found 332.5.

[00225] Step 4: (2*S*,4*R*)-1-Benzyl 2-methyl 4-hydroxy-4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate is prepared from (2*S*,4*R*)-1-benzyl 2-methyl 4-hydroxy-4-(hydroxymethyl)pyrrolidine-1,2-dicarboxylate following Method X (yield = 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.21 (m, 5 H), 5.32-4.97 (m, 2 H), 4.61-4.42 (m, 1 H), 3.80-3.28 (m, 10 H), 2.69-1.87 (m, 2 H).

[00226] Step 5: (2*S*,4*R*)-1-(Benzyloxycarbonyl)-4-hydroxy-4-(methoxymethyl)pyrrolidine-2-carboxylic acid is prepared from (2*S*,4*R*)-1-benzyl 2-methyl 4-hydroxy-4-(methoxymethyl)pyrrolidine-1,2-dicarboxylate following Method Y (yield = 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.18 (m, 5 H), 5.23-5.05 (m, 2H), 4.65-4.47 (m, 1 H), 3.78-3.28 (m, 7 H), 2.46-1.97 (m, 3H).

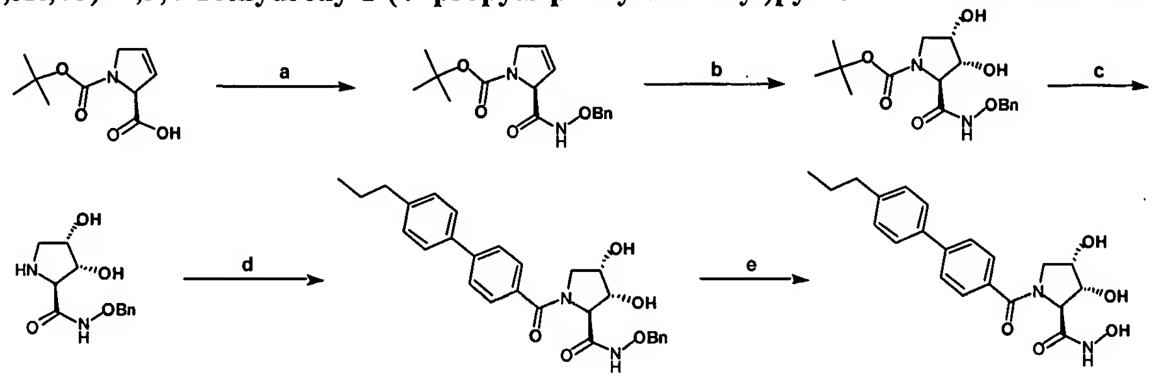
[00227] Step 6: (2*S*,4*R*)-Benzyl 4-hydroxy-4-(methoxymethyl)-2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)pyrrolidine-1-carboxylate is prepared from (2*S*,4*R*)-1-(benzyloxycarbonyl)-4-hydroxy-4-(methoxymethyl)pyrrolidine-2-carboxylic acid and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine following Method G (yield = 59%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.57-7.18 (m, 5 H), 5.33-5.07 (m, 2 H), 4.64-4.45 (m, 1 H), 4.09-3.21 (m, 7 H), 2.44-1.98 (m, 3 H); ESI(+) calcd. for $C_{15}H_{18}NO_6$ (308.11), found 308.0

[00228] Step 7: (2*S*,4*R*)-4-Hydroxy-4-(methoxymethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy) pyrrolidine-2-carboxamide is prepared from (2*S*,4*R*)-benzyl 4-hydroxy-4-(methoxymethyl)-2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)pyrrolidine-1-carboxylate following Method Z (yield = 99%). ESI(+) calcd. for $C_{12}H_{23}N_2O_5$ (275.16), found 275.2.

[00229] Step 8: (2*S*,4*R*)-4-Hydroxy-4-(methoxymethyl)-1-(4'-propylbiphenylcarbonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidine-2-carboxamide from 4-(4-propylphenyl) benzoic acid is prepared from (2*S*,4*R*)-4-hydroxy-4-(methoxymethyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidine-2-carboxamide and 4-(4-propylphenyl)benzoic acid following Method EE (yield = 85%). ESI(-) calcd. for $C_{28}H_{35}N_2O_6$ (495.25), found 495.2.

[00230] Step 9: (2*S*,4*R*)-*N*,4-Dihydroxy-4-(methoxymethyl)-1-(4'-propylbiphenylcarbonyl) pyrrolidine-2-carboxamide is prepared from (2*S*,4*R*)-4-hydroxy-4-(methoxymethyl)-1-(4'-propylbiphenylcarbonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidine-2-carboxamide following method AA, and purified by preparative-HPLC (yield = 30%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.72 (s, 1H), 8.86 (s, 1 H), 7.80-7.48 (m, 6 H), 7.26-7.38 (m, 2 H), 5.01 (s, 1 H), 4.49 (t, *J* = 9.6 Hz, 1 H), 3.78 (d, *J* = 10.5 Hz, 1 H), 3.27-2.42 (m, 7 H), 2.07-1.91 (m, 2 H), 1.73-1.55 (m, 2 H), 1.33-1.20 (m, 1 H), 0.91 (m, 3 H); ESI(+) calcd. for $C_{23}H_{28}N_2NaO_5$ (435.19), found 435.1.

Example 10
(2*S*,3*R*,4*S*)-*N*,3,4-Trihydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00231] **Scheme E**: Reagents and conditions. (a) O-benylhydroxylamine, HATU, DIEA, DMF, rt, 18 h; (b) OsO_4, NMO, t-BuOH, acetone, water, rt, 18 h; (c) TFA, DCM, rt, 2 h; (d) 4-(4-n-propylphenyl)benzoic acid, HATU, DIEA, DMF, rt, 18 h; (e) 10% Pd/C, EtOH, H_2, rt, 8 h.

[00232] Step 1: (2*S*)-*tert*-Butyl 2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate is prepared from (*S*)-1-(*tert*-butoxycarbonyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (Boc-3,4-dehydro-proline) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine following Method G (yield = 86%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.38 (s, 0.5 H), 8.46 (s, 0.5 H), 7.52-7.22 (m, 5 H), 6.01-5.77 (m, 2 H), 5.04-4.79 (m, 3 H), 4.38-3.99 (m, 2 H), 1.43 (s, 9 H).

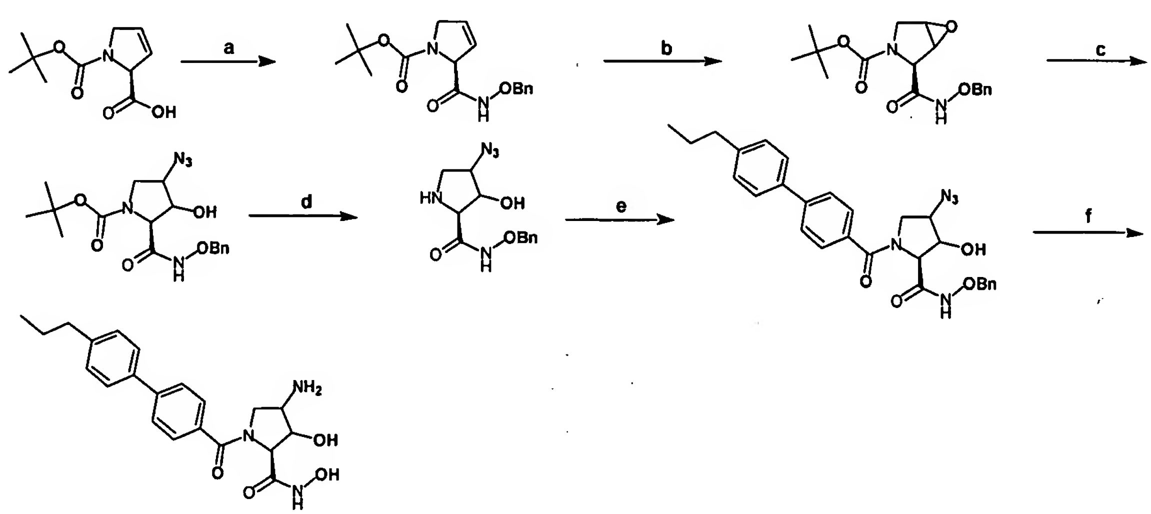
[00233] Step 2: (2*S*,3*R*,4*S*)-*tert*-Butyl 3,4-dihydroxy-2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)pyrrolidine-1-carboxylate is prepared from (2*S*)-*tert*-butyl 2-(tetrahydro-2H-pyran-2-yloxycarbamoyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate following Method W (yield = 69%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.79 (s, 1 H), 7.48-7.28 (m, 5 H), 5.01-4.83 (m, 2 H), 4.47-3.41 (m, 5 H), 1.83-1.28 (m, 11 H).

[00234] Step 3: (2*S*,3*R*,4*S*)-3,4-dihydroxy-N-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidine-2-carboxamide is prepared from (2*S*,3*R*,4*S*)-*tert*-butyl 3,4-dihydroxy-2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)pyrrolidine-1-carboxylate following Method AA (yield = 100%). ESI(+) calcd. for $C_{12}H_{17}N_2O_4$ (253.12), found 253.2.

[00235] Step 4: (2*S*,3*R*,4*S*)-3,4-Dihydroxy-1-(4'-propylbiphenylcarbonyl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidine-2-carboxamide is prepared from (2*S*,3*R*,4*S*)-3,4-dihydroxy-*N*-(tetrahydro-2*H*-pyran-2-yloxy)pyrrolidine-2-carboxamide and 4-(4-propylphenyl)benzoic acid following Method G (yield = 93%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.70-6.90 (m, 13 H), 4.97-4.78 (m, 2 H), 4.66-4.37 (m, 2 H), 4.30-4.07 (m, 2 H), 3.83-3.45 (m, 2 H), 2.96-2.78 (m, 2 H), 2.74-2.48 (m, 2 H), 1.90-1.53 (m, 2 H), 1.13-0.85 (m, 3 H).

[00236] Step 5: (2*S*,3*R*,4*S*)-*N*,3,4-trihydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide is prepared from (2*S*,3*R*,4*S*)-3,4-dihydroxy-1-(4'-propylbiphenylcarbonyl)-*N*-(tetrahydro-2H-pyran-2-yloxy)pyrrolidine-2-carboxamide following Method AA. The compound was purified by preparative-HPLC (yield = 32%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.78 (s, 1 H), 7.87-7.46 (m, 6 H), 7.40-7.19 (m, 2 H), 4.26-3.22 (m, 7 H), 2.70-2.37 (m, 2 H), 1.74-1.46 (m, 2 H), 1.03-0.76 (m, 3 H); ESI(-) calcd. for $C_{21}H_{23}N_2O_5$ (383.16), found 383.2.

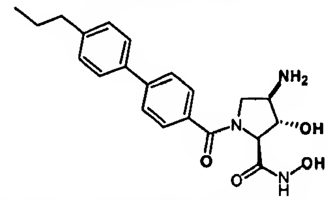
[00237] 4-Amino-*N*,3-dihydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide was prepared following the steps utilized in **Scheme-E.**



[00238] Scheme F : Reagents and conditions. (a) O-benylhydroxylamine, HATU, DIEA, DMF, rt, 18 h; (b) OsO_4, NMO, t-BuOH, acetone, water, rt, 18 h; (c) sodium azide, DMF, water,

80 °C, 18 h; (d) TFA, DCM, rt, 2 h; (e) 4-(4-n-propylphenyl)benzoic acid, HATU, DIEA, DMF, rt, 18 h; (f) 10% Pd/C, EtOH, H_2, rt, 8 h.

Example 11
(2*S*,3*S*,4*R*)-4-Amino-*N*,3-dihydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00239] Step 1: (2*S*)-*tert*-Butyl 2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate is prepared from (*S*)-1-(*tert*-butoxycarbonyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (Boc-3,4-dehydro-proline) and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine following Method G (yield = 86%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.38 (s, 0.5 H), 8.46 (s, 0.5 H), 7.52-7.22 (m, 5 H), 6.01-5.77 (m, 2 H), 5.04-4.79 (m, 3 H), 4.38-3.99 (m, 2 H), 1.43 (s, 9 H).

[00240] Step 2: (1*R*,2*S*,5*S*)-*tert*-Butyl 2-(benzyloxycarbamoyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate is prepared from (2*S*)-*tert*-butyl 2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate following Method CC. (yield = 31%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.83-9.00 (m, 1 H), 8.14-7.26 (m, 5 H), 5.22-4.79 (m, 2 H), 4.54-3.24 (m, 5 H), 1.38 (s, 9 H); ESI(-) calcd. for $C_{17}H_{21}N_2O_5$ (333.15), found 333.2.

[00241] Step 3: (2*S*,3*R*,4*R*)-*tert*-Butyl 4-azido-2-(benzyloxycarbamoyl)-3-hydroxypyrrolidine-1-carboxylate is prepared from (1*R*,2*S*,5*S*)-*tert*-butyl 2-(benzyloxycarbamoyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate following Method DD (yield = 79%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.78-8.88 (m, 1 H), 7.78-7.22 (m, 5 H), 5.06-3.64 (m, 7 H), 3.48-3.18 (m, 1 H), 1.37 (m, 9 H); ESI(-) calcd. for $C_{17}H_{22}N_5O_5$ (376.16), found 376.2.

[00242] Step 4: (2*S*,3*R*,4*R*)-4-Azido-*N*-(benzyloxy)-3-hydroxypyrrolidine-2-carboxamide is prepared from (2*S*,3*R*,4*R*)-*tert*-butyl 4-azido-2-(benzyloxycarbamoyl)-3-hydroxypyrrolidine-1-

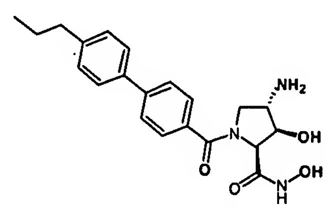
carboxylate following Method AA (yield = 100%). ESI(+) calcd. for $C_{12}H_{16}N_5O_3$ (287.13), found 287.2.

[00243] Step 5: (2*S*,3*R*,4*R*)-4-Azido-*N*-(benzyloxy)-3-hydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide is prepared from (2*S*,3*R*,4*R*)-4-azido-*N*-(benzyloxy)-3-hydroxypyrrolidine-2-carboxamide and 4-(4-propylphenyl)benzoic acid following Method G (yield = 84%). ESI(-) calcd. for $C_{28}H_{28}N_5O_4$ (498.21), found 498.2.

[00244] Step 6: (2*S*,3*S*,4*R*)-4-Amino-*N*,3-dihydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide is prepared from (2*S*,3*R*,4*R*)-4-azido-*N*-(benzyloxy)-3-hydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide following Method Z. The compound was purified by preparative-HPLC (yield = 8%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.23-9.10 (m, 1 H), 7.74-7.38 (m, 8 H), 7.34-7.16 (m, 2 H), 6.48-6.16 (m, 1 H), 4.20-3.38 (m, 6 H), 2.64-2.40 (m, 2 H), 1.61-1.42 (m, 2 H), 0.94-0.69 (m, 3 H); ESI(+) calcd. for $C_{21}H_{26}N_3O_4$ (384.19), found 384.2.

Example 12

(2*S*,3*R*,4*S*)-4-Amino-*N*,3-dihydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide



[00245] Step 1: (2*S*)-*tert*-Butyl 2-(tetrahydro-2*H*-pyran-2-yloxycarbamoyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate is prepared from (*S*)-1-(*tert*-butoxycarbonyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (Boc-3,4-dehydro-proline) and *O*-(tetrahydro-2H-pyran-2-yl)hydroxylamine following Method G (yield = 86%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.38 (s, 0.5 H), 8.46 (s, 0.5 H), 7.52-7.22 (m, 5 H), 6.01-5.77 (m, 2 H), 5.04-4.79 (m, 3 H), 4.38-3.99 (m, 2 H), 1.43 (s, 9 H).

[00246] Step 2: (1*S*,2*S*,5*R*)-*tert*-Butyl 2-(benzyloxycarbamoyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate is prepared from (2*S*)-*tert*-butyl 2-(tetrahydro-2*H*-pyran-

2-yloxycarbamoyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate following Method CC (yield = 12%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 8.80-8.41 (m, 1 H), 8.13-7.26 (m, 5 H), 5.16-4.78 (m, 2 H), 4.44-3.37 (m, 5 H), 1.38 (s, 9 H); ESI(-) calcd. for $C_{17}H_{21}N_2O_5$ (333.15), found 333.2.

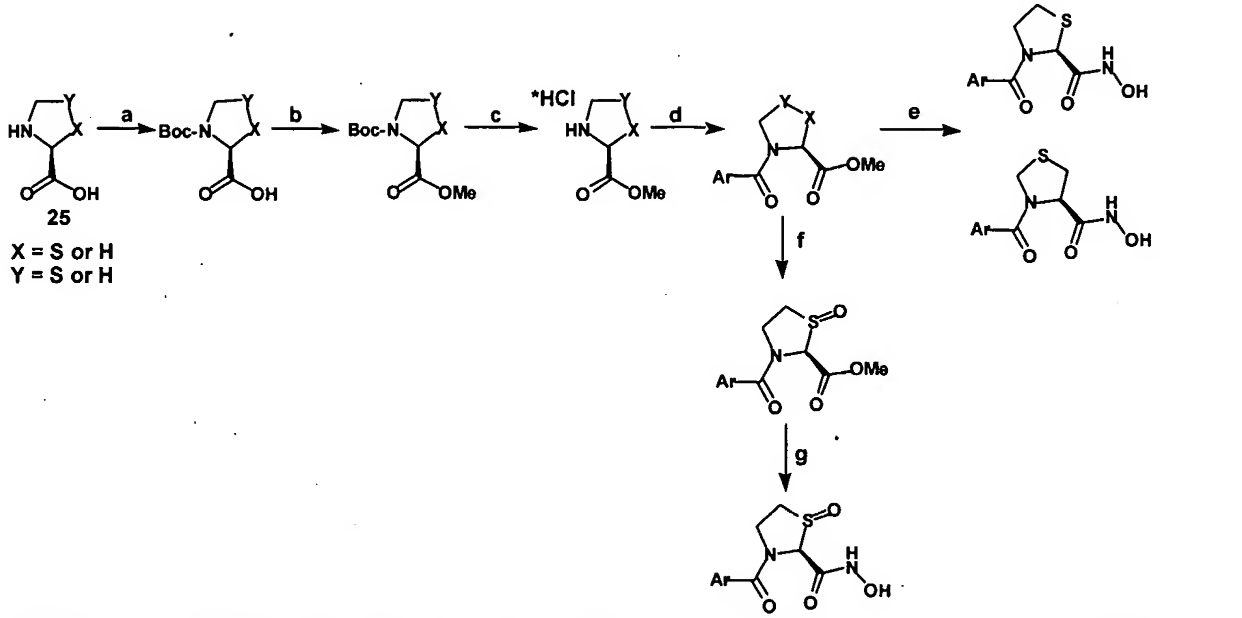
[00247] Step 3: (2*S*,3*S*,4*S*)-*tert*-Butyl 4-azido-2-(benzyloxycarbamoyl)-3-hydroxypyrrolidine-1-carboxylate is prepared from (1*S*,2*S*,5*R*)-*tert*-butyl 2-(benzyloxycarbamoyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate following Method DD (yield = 66%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 9.80-8.86 (m, 1 H), 7.81-7.21 (m, 5 H), 5.05-3.65 (m, 7 H), 3.48-3.17 (m, 1 H), 1.37 (m, 9 H); ESI(-) calcd. for $C_{17}H_{22}N_5O_5$ (376.16), found 376.2.

[00248] Step 4: (2*S*,3*S*,4*S*)-4-Azido-*N*-(benzyloxy)-3-hydroxypyrrolidine-2-carboxamide is prepared from (2*S*,3*S*,4*S*)-*tert*-butyl 4-azido-2-(benzyloxycarbamoyl)-3-hydroxypyrrolidine-1-carboxylate following Method AA (yield = 100%). ESI(+) calcd. for $C_{12}H_{16}N_5O_3$ (287.13), found 287.2.

[00249] Step 5: (2*S*,3*S*,4*S*)-4-Azido-*N*-(benzyloxy)-3-hydroxy-1-(4'-propylbiphenylcarbonyl) pyrrolidine-2-carboxamide is prepared from (2*S*,3*S*,4*S*)-4-azido-*N*-(benzyloxy)-3-hydroxypyrrolidine-2-carboxamide and 4-(4-propylphenyl)benzoic acid following Method G(yield = 105%). ESI(-) calcd. for $C_{28}H_{28}N_5O_4$ (498.21), found 498.2.

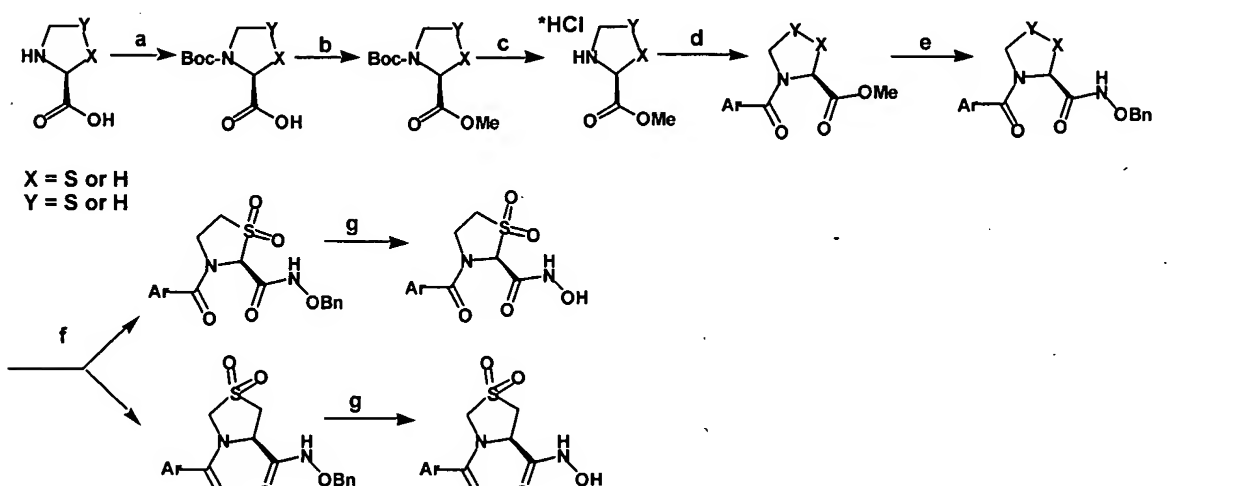
[00250] Step 6: (2*S*,3*R*,4*S*)-4-Amino-*N*,3-dihydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide is prepared from (2*S*,3*S*,4*S*)-4-azido-*N*-(benzyloxy)-3-hydroxy-1-(4'-propylbiphenylcarbonyl)pyrrolidine-2-carboxamide following Method Z (yield = 10%). The compound was purified by preparative-HPLC.. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.66 (s, 0.5 H), 8.97 (s, 0.5 H), 8.40-7.98 (m, 2 H), 7.81-7.42 (m, 6 H), 7.38-7.16 (m, 2 H), 6.62-6.17 (m, 1 H), 4.60-3.38 (m, 6 H), 2.66-2.40 (m, 2 H), 1.65-1.48 (m, 2 H), 1.02-0.77 (m, 3 H); ESI(+) calcd. for $C_{21}H_{26}N_3O_4$ (384.19), found 384.4.

General synthesis of 1-Aroyl Thiaproline and Thiazolidine Sulfoxide Hydroxamate Derivatives.



[00251] **Scheme G:** Reagents and conditions. (a) Protection (Boc_2O, base); (b) Methyl ester formation ($TMSCHN_2$, MeOH); (c) Deprotection (4M HCl/Dioxane); (d) Coupling (ArCOOH, HATU, DIEA, DMF); (e) Hydroxamate formation ($NH_2OH.HCl$, NaOMe, MeOH); (f) Oxidation (MCPBA, DCM); (g) Hydroxamate formation (50% NH_2OH, KCN(cat.), MeOH).

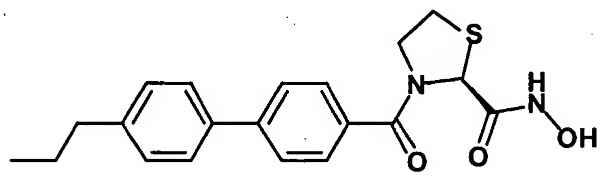
General synthesis of 1-Aroyl Thiazolidinesulfone Hydroxamate Derivatives



[00252] **Scheme H:** Reagents and conditions. (a) Protection (Boc_2O, base); (b) Methyl ester formation ($TMSCHN_2$, MeOH); (c) Deprotection (4M HCl/Dioxane); (d) Coupling

(ArCOOH, HATU, DIEA, DMF); (e) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene); (f) Oxidation (MCPBA, DCM); (g) Hydroxamate formation (10% $Pd(OH)_2$, EtOH).

Example 13
(S)-N-Hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxamide



[00253] Step 1: (S)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate was prepared from (S)-3-(*tert*-butoxycarbonyl)thiazolidine-2-carboxylic acid following Method B using the commercially available Boc-protected carboxylic acid (yield = 81%). ES-MS: calcd. for $C_{10}H_{17}NO_4S$ (247.31)

[00254] Step 2: (S)-methyl thiazolidine-2-carboxylate hydrochloride salt was prepared from (S)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 5.67 (d, J = 1.65 Hz, 1H), 3.96 – 3.95 (d, J = 1.65 Hz, 1H), 3.75 – 3.70 (m, 2H), 3.4 – 3.35 (m, 2H). ES-MS: calcd. for $C_5H_9NO_2S$ (147.2); found: 148.1[M+H]..

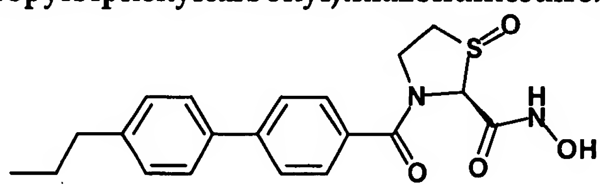
[00255] Step 3: (S)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate was prepared from (S)-methyl thiazolidine-2-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 42%). ^{1}H NMR (DMSO-d_6): 7.76 – 7.73 (d, J = 8.24 Hz, 2H), 7.64 – 7.61 (d, J = 8.24 Hz, 4H), 7.32 – 7.29 (d, J = 8.24 Hz, 2H), 5.575 (bs, 1H), 4.0 (bs, 1H), 3.89 – 3.82 (m, 1H), 3.7 (s, 3H), 3.18 – 3.14 (t, J = 6.32 & 6.04 Hz, 2H), 2.62 – 2.56 (t, J = 7.14 & 7.97 Hz, 2H), 1.67 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.27 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_3S$ (369.48) found: 392.2 [M+Na]..

[00256] Step 4: (S)-*N*-hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxamide was prepared (S)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate from following Method H (yield = 15%). ^{1}H NMR (DMSO-d_6): 10.76 (bs, 1H), 9.05 (bs, 1H), 7.74 – 7.72 (d, J = 8.24 Hz, 2H), 7.63 – 7.61 (d, J = 8.24 Hz, 4H), 7.31 – 7.29 (d, J = 7.97 Hz, 2H), 5.525 (bs, 1H), 3.89 (bs, 1H), 3.43 (bs, 1H), 3.17 – 3.06 (m, 1H), 2.62 – 2.57 (t, J = 7.14 & 7.97 Hz, 2H), 1.68 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.42 Hz, 3H).

HPLC: Rt = 6.09 min following Method R.

ES-MS: calcd. for $C_{20}H_{22}N_2O_3S$ (370.47) found: 371 [M+H]..

Example 14
(*S*)-*N*-Hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfoxide-2-carboxamide



[00257] Step 1: (*S*)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate was prepared from (*S*)-3-(*tert*-butoxycarbonyl)thiazolidine-2-carboxylic acid following Method B using the commercially available Boc-protected carboxylic acid (yield = 81%). ES-MS: calcd. for $C_{10}H_{17}NO_4S$ (247.31)

[00258] Step 2: (*S*)-methyl thiazolidine-2-carboxylate hydrochloride salt was prepared from (S)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate following Method F (quantitative yield) ^{1}H NMR (DMSO-d_6): 5.67 (d, J = 1.65 Hz, 1H), 3.96 – 3.95 (d, J = 1.65 Hz, 1H), 3.75 – 3.70 (m, 2H), 3.4 – 3.35 (m, 2H). ES-MS: calcd. for $C_5H_9NO_2S$ (147.2); found: 148.1[M+H]..

[00259] Step 3: (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate was prepared from (*S*)-methyl thiazolidine-2-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 42%). ^{1}H NMR (DMSO-d_6): 7.76 – 7.73 (d, J = 8.24 Hz, 2H), 7.64 – 7.61 (d, J = 8.24 Hz, 4H), 7.32 – 7.29 (d, J = 8.24 Hz, 2H), 5.575 (bs, 1H), 4.0 (bs, 1H), 3.89 – 3.82 (m, 1H), 3.7 (s, 3H), 3.18 – 3.14 (t, J = 6.32 & 6.04 Hz,

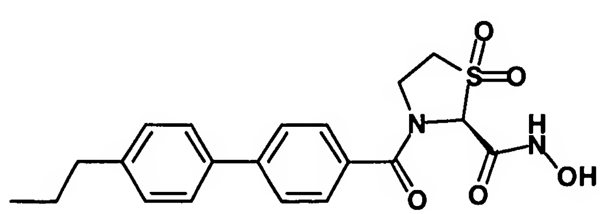
2H), 2.62 – 2.56 (t, J = 7.14 & 7.97 Hz, 2H), 1.67 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.27 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_3S$ (369.48) found: 392.2 [M+Na].

[00260] Step 4: (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidinesulfoxide-2-carboxylate was prepared from (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate following Method S (yield = 20%-30%). The two isomers were isolated as a mixture in the ratio of 2:1 by NMR. ^{1}H NMR (DMSO-d$_6$): 8.09 – 8.07 (m, 2H), 7.97 – 7.7 (m, 4H), 7.52 – 7.49 (d, J = 7.97 Hz, 2H), 5.96 (bs, 0.33H), 5.94 (bs, 0.66H), 4.46 (bs, 1H), 3.95 (bs, 3H), 3.41 – 3.21 (m, 2H), 2.82 – 2.77 (t, J = 7.42 & 7.69 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 Hz, 3H). HPLC: Rt = 6.37 & 6.39 min following Method R.

ES-MS: calcd. for $C_{21}H_{23}NO_4S$ (385.48) found: 408.1 [M+Na]..

[00261] Step 5: (S)-N-hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfoxide-2-carboxamide was prepared from (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)-2-thiazolidinesulfoxide-2-carboxylate following Method T (yield = 40%). This was a diastereomeric mixture in the ratio of 2:1. ^{1}H NMR (DMSO-d$_6$): 11.52 – 11.28 (d, 1H), 9.55 (bs, 1H), 7.97 – 7.94 (d, J = 7.97 Hz, 2H), 7.84 – 7.82 (d, J = 8.24 Hz, 4H), 7.52 – 7.49 (d, J = 7.97 Hz, 2H), 5.84 (bs, 0.33H), 5.45 9bs, 0.66H), 4.39 (bs, 2H), 3.25 (bs, 2H), 2.82 – 2.77 (t, J = 7.42 & 7.69 Hz, 2H), 1.94 – 1.42 (m, 2H), 1.13 – 1.08 (t, J = 7.42 Hz, 3H). HPLC: Rt = 5.64 min following Method R. ES-MS: calcd. for $C_{20}H_{22}N_2O_4S$ (386.47) found: 385.2 [M-H]..

Example 15
(*S*)-*N*-Hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide



NB1:662111.3

[00262] Step 1: (*S*)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate was prepared from (*S*)-3-(*tert*-butoxycarbonyl)thiazolidine-2-carboxylic acid following Method B using the commercially available Boc-protected carboxylic acid (yield = 81%). ES-MS: calcd. for $C_{10}H_{17}NO_4S$ (247.31).

[00263] Step 2: (*S*)-methyl thiazolidine-2-carboxylate hydrochloride salt was prepared from (*S*)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate following Method F (quantitative yield). ^1H NMR (DMSO-d_6): 5.67 (d, J = 1.65 Hz, 1H), 3.96 – 3.95 (d, J = 1.65 Hz, 1H), 3.75 – 3.70 (m, 2H), 3.4 – 3.35 (m, 2H). ES-MS: calcd. for $C_5H_9NO_2S$ (147.2); found: 148.1[M+H].

[00264] Step 3: (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate was prepared from (*S*)-methyl thiazolidine-2-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 42%). ^1H NMR (DMSO-d_6): 7.76 – 7.73 (d, J = 8.24 Hz, 2H), 7.64 – 7.61 (d, J = 8.24 Hz, 4H), 7.32 – 7.29 (d, J = 8.24 Hz, 2H), 5.575 (bs, 1H), 4.0 (bs, 1H), 3.89 – 3.82 (m, 1H), 3.7 (s, 3H), 3.18 – 3.14 (t, J = 6.32 & 6.04 Hz, 2H), 2.62 – 2.56 (t, J = 7.14 & 7.97 Hz, 2H), 1.67 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.27 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_3S$ (369.48) found: 392.2 [M+Na].

[00265] Step 4: (*S*)-N-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxamide was prepared from (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate following Method I (yield = 80%). ^1H NMR (DMSO-d_6): 11.38 (bs, 1H), 7.7 – 7.6 (m, 5H), 7.36 – 7.3 (m, 8H), 5.75 (bs, 1H), 4.78 (bs, 2H), 3.89 (bs, 1H), 3.3 – 3.1 (m, 2H), 2.62 – 2.57 (t, J = 7.42 & 7.69 Hz, 2H), 1.67 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.115 min following Method R. ES-MS: calcd. for $C_{27}H_{28}N_2O_3S$ (460) found: 461 [M+H].

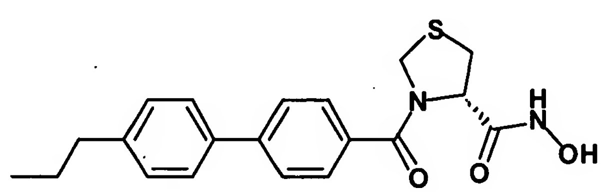
[00266] Step 5: (*S*)-*N*-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide was prepared from (*S*)-N-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidine-2-

carboxamide following Method S (yield = 60%). ^{1}H NMR (DMSO-d_6): 11.96 (bs, 1H), 7.77 – 7.52 (m, 6H), 7.37 – 7.3 (m, 7H), 5.27 (bs, 1H), 4.80 (bs, 2H), 4.07 – 3.96 (m, 2H), 3.79 – 3.75 (t, J = 6.32 Hz, 1H), 3.56 – 3.38 (m, 1H), 2.63 – 2.57 (t, J = 8.24 & 7.14 Hz, 2H), 1.68 – 1.56 (m, 2H), 0.93 – 0.88 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 6.97 min following Method R.

ES-MS: calcd. for $C_{27}H_{28}N_2O_5S$ (492.59) found: 493.2 [M+H].

[00267] Step 6: (*S*)-*N*-hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide was prepared from (*S*)-*N*-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide following Method P (yield = 30%). The compound was isolated as containing 15%-20% of the opposite isomer, as analyzed by HPLC and using a chiral column. ^{1}H NMR (DMSO-d_6): 11.47 (bs, 1H), 9.68 (bs, 1H), 7.98 – 7.95 (d, J = 8.24 Hz, 2H), 7.85 – 7.82 (d, J = 7.97 Hz, 4H), 7.52 – 7.49 (d, J = 7.97 Hz, 2H), 5.5 (bs, 1H), 4.27 (bs, 1H), 3.92 (bs, 1H), 3.69 – 3.65 (m, 2H), 2.82 – 2.77 (t, J = 7.42 & 7.69 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.13 – 1.08 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.92 min following Method R. ES-MS: calcd. for $C_{20}H_{22}N_2O_5S$ (402.469) found: 401.2 [M-H].

Example 16
(*S*)-*N*-Hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxamide



[00268] Step 1: (*S*)-3-*tert*-butyl 4-methyl thiazolidine-3,4-dicarboxylate was prepared from (*S*)-3-(*tert*-butoxycarbonyl)thiazolidine-4-carboxylic acid following Method B using the commercially available Boc-protected carboxylic acid (yield = 92%)

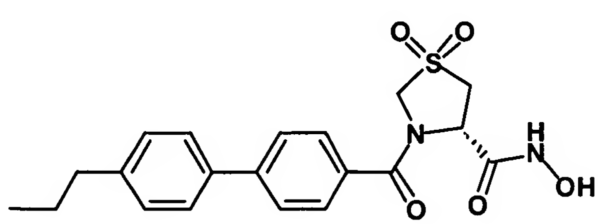
^{1}H NMR (DMSO-d_6): 4.94 – 4.81 (d, 1H), 4.74 – 4.68 (d, J = 9.07 Hz, 1H), 4.56 – 4.54 (d, J = 7.97 Hz, 1H), 3.86 (s, 3H), 3.61 – 3.58 (d, J = 7.97 Hz, 1H), 3.34 – 3.31 (d, J = 7.14 Hz, 1H), 1.6 – 1.54 (d, J = 15.9 HZ, 9H). HPLC: Rt = 5.125 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_4S$ (247.09); found: 270 [M+Na].

[00269] Step 2: (*S*)-methyl thiazolidine-4-carboxylate hydrochloride salt was prepared from (S)-3-*tert*-butyl 4-methyl thiazolidine-3,4-dicarboxylate following Method F (quantitative yield) ^{1}H NMR (DMSO-d_6): 4.77 – 4.72 (t, J = 6.87 & 6.59 Hz, 1H), 4.33 – 4.23 (dd, J = 9.6 Hz, 1H), 3.76 (d, 3H), 3.39 – 3.23 (m, 2H). ES-MS: calcd. for $C_5H_9NO_2S$ (147.2); found: 148.1 [M+H].

[00270] Step 3: (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-4-carboxylate was prepared from (*S*)-methyl thiazolidine-4-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 75%). ^{1}H NMR (DMSO-d_6): 7.95 – 7.93 (d, J = 7.97 Hz, 2H), 7.83 – 7.80 (d, J = 8.24 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 5.25 (bs, 1H), 4.85 – 4.83 (d, J = 7.14 Hz, 2H), 3.88 (m, 3H), 3.76 – 3.66 (m, 1H), 3.49 – 3.38 (m, 1H), 2.81 – 2.76 (t, J = 7.42 & 7.69 Hz, 2H), 1.85 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.19 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_3S$ (369.48) found: 392 [M+Na].

[00271] Step 4: (*S*)-*N*-hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidine-4-carboxamide was prepared from (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-4-carboxylate following Method H (yield = 40%). ^{1}H NMR (DMSO-d_6): 10.84 (bs, 1H), 7.75 – 7.73 (d, J = 7.97 Hz, 2H), 7.64 – 7.61 (d, J = 7.97 Hz, 4H), 7.32 – 7.29 (d, J = 8.24 Hz, 2H), 4.86 (bs, 1H), 4.65 (bs, 2H), 3.35 (bs, 1H), 3.13 – 3.07 (dd, J = 5.49 Hz, 1H), 2.62 – 2.57 (t, J = 7.42 & 7.69 Hz, 2H), 1.68 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.09 min following Method R. ES-MS: calcd. for $C_{20}H_{22}N_2O_3S$ (370.47) found: 371.4 [M+H]..

Example 17
(*S*)-*N*-Hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-4-carboxamide



[00272] Step 1: (*S*)-3-*tert*-butyl 4-methyl thiazolidine-3,4-dicarboxylate was prepared from (*S*)-3-(*tert*-butoxycarbonyl)thiazolidine-4-carboxylic acid following Method B using the commercially available Boc-protected carboxylic acid (yield = 92%). ^{1}H NMR (DMSO-d_6): 4.94 – 4.81 (d, 1H), 4.74 – 4.68 (d, J = 9.07 Hz, 1H), 4.56 – 4.54 (d, J = 7.97 Hz, 1H), 3.86 (s,3H), 3.61 – 3.58 (d, J = 7.97 Hz, 1h), 3.34 – 3.31 (d, J = 7.14 Hz, 1H), 1.6 – 1.54 (d, J = 15.9 HZ, 9H). HPLC: Rt = 5.125 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_4S$ (247.09); found: 270[M+Na]..

[00273] Step 2: (*S*)-methyl thiazolidine-4-carboxylate hydrochloride salt was prepared from (*S*)-3-*tert*-butyl 4-methyl thiazolidine-3,4-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 4.77 – 4.72 (t, J = 6.87 & 6.59 Hz, 1H), 4.33 – 4.23 (dd, J = 9.6 Hz, 1H), 3.76 (d, 3H), 3.39 – 3.23 (m, 2H), ES-MS: calcd. for $C_5H_9NO_2S$ (147.2); found: 148.1 [M+H]..

[00274] Step 3: (*S*)-methyl 3-(1-(4'-propylbiphenyl carbonyl)thiazolidine-4-carboxylate was prepared from (*S*)-methyl thiazolidine-4-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 75%) ^{1}H NMR (DMSO-d_6): 7.95 – 7.93 (d, J = 7.97 Hz, 2H), 7.83 – 7.80 (d, J = 8.24 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 5.25 (bs, 1H), 4.85 – 4.83 (d, J = 7.14 Hz, 2H), 3.88 (m, 3H), 3.76 – 3.66 (m, 1H), 3.49 – 3.38 (m, 1H), 2.81 – 2.76 (t, J = 7.42 & 7.69 Hz, 2H), 1.85 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.19 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_3S$ (369.48) found: 392 [M+Na].

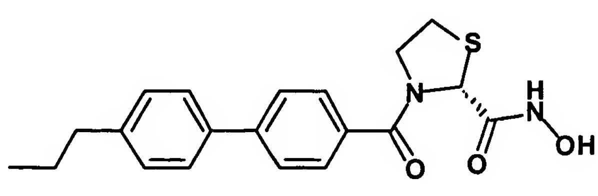
[00275] Step 4: (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-4-carboxylate was prepared from (*S*)-methyl 3-(1-(4'-propylbiphenyl carbonyl)thiazolidine-4-carboxylate following Method S (yield = 70%). ^{1}H NMR (DMSO-d_6): 7.8 – 7.77 (d, J = 8.24 Hz, 2H), 7.65 – 7.53 (m, 4H), 7.33 – 7.31 (d, J = 7.69 Hz, 2H), 5.44 (bs, 1H), 4.91 – 4.8 (d, 2H), 4.0 – 3.97 (m, 1H), 3.75 – 3.69 (m, 1H), 3.73 (s, 3H), 2.62 – 2.57 (t, J = 7.42 Hz, 2H), 1.68 –

1.56 (m, 2H), 0.93 – 0.88 (m, 3H). HPLC: Rt = 6.78 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_5S$ (401.48) found: 424 [M+Na].

[00276] Step 5: (*S*)-*N*-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-4-carboxamide was prepared from (*S*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-4-carboxylate following Method I (yield = 60%). ^{1}H NMR (DMSO-d_6): 7.79 – 7.76 (d, J = 8.24 Hz, 2H), 7.66 – 7.63 (d, J = 7.97 Hz, 4H), 7.4 – 7.3 (m, 7H), 5.75 (bs, 1H), 4.81 (bs, 4H), 3.86 – 3.79 (dd, J = 8.79 Hz, 1H), 3.56 – 3.41 (m, 1H), 2.63 – 2.58 (t, J = 7.42 & 7.69 Hz, 2H), 1.68 – 1.56 (m, 2H), 0.93 – 0.89 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.97 min following Method R. ES-MS: calcd. for $C_{27}H_{28}N_2O_5S$ (492.59) found: 515.2 [M+Na].

[00277] Step 6: (*S*)-*N*-hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-4-carboxamide was prepared from (*S*)-*N*-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-4-carboxamide following Method P (yield = 80%). ^{1}H NMR (DMSO-d_6): 11.07 (bs, 1H), 9.2 (bs, 1H), 7.8 – 7.76 (d, J = 8.24 Hz, 2H), 7.65 – 7.63 (d, J = 8.24 Hz, 4H), 7.32 – 7.3 (d, J = 7.97 Hz, 2H), 5.2 (bs, 1H), 4.85 (bs, 2H), 3.9 – 3.83 (m, 1H), 3.47 – 3.41 (m, 1H), 2.62 – 2.57 (t, J = 7.42 & 7.69 Hz, 2H), 1.68 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.99 min following Method R. ES-MS: calcd. for $C_{20}H_{22}N_2O_5S$ (402.47) found: 401.4 [M+H].

Example 18
(*R*)-*N*-Hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxamide



[00278] Step 1: (*R*)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate was prepared from (*R*)-3-(*tert*-butoxycarbonyl)thiazolidine-2-carboxylic acid following Method B using the commercially available Boc-protected carboxylic acid following Method F (yield = 94%). ^{1}H

NMR (DMSO-d_6): 5.43 – 5.37 (d, 1H), 3.96 (bs, 2H), 3.87 (s, 2H), 3.27 (bs, 2H), 1.59 –1.53 (d, 9H). HPLC: Rt = 5.31 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_4S$ (247.09); found: 269.9 [M+Na].

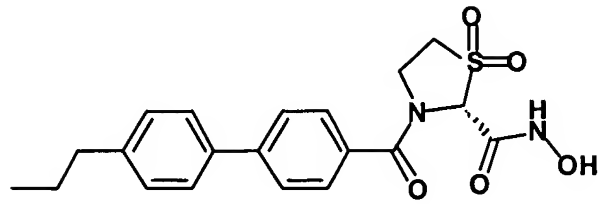
[00279] Step 2: (*R*)-methyl thiazolidine-2-carboxylate hydrochloride salt was prepared from (*R*)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 5.66 (s, 1H), 3.95 (s, 3H), 3.74 – 3.70 (t, J = 6.59 & 6.32 Hz, 2H), 3.39 – 3.37 (m, 2H). ES-MS: calcd. for $C_5H_9NO_2S$ (147.2); found: 148.1 [M+H].

[00280] Step 3: (*R*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate was prepared from (*R*)-methyl thiazolidine-2-carboxylate following Method G (yield = 92%)

^{1}H NMR (DMSO-d_6): 8.24 – 8.17 (m, 2H), 7.98 – 7.80 (m, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 5.77 (bs, 1H), 4.2 (bs, 1H), 4.09 – 4.01 (m, 1H), 3.9 (s, 3H), 3.37 – 3.33 (t, J = 6.04 & 6.32 Hz, 2H), 2.81 – 2.76 (t, J = 7.97 & 7.42 Hz, 2H), 1.87 – 1.74 (m, 2H), 1.12 – 1.07 (m, 3H). HPLC: Rt = 7.16 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_3S$ (369.48) found: 370 [M+H].

[00281] Step 4: (*R*)-*N*-hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxamide was prepared from (*R*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate following Method H (yield = 20%) ^{1}H NMR (DMSO-d_6): 10.9 (bs, 1H), 9.29 (bs, 1H), 7.94 – 7.91 (d, J = 8.24 Hz, 2H), 7.83 – 7.80 (d, J = 8.24 Hz, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 5.72 (bs, 1H), 4.08 (bs, 1H), 3.77 (bs, 1H), 3.42 – 3.35 (m, 2H), 2.81 – 2.76 (t, J = 7.42 & 7.69 Hz, 2H), 1.87 – 1.74 (m, 2H), 1.12 – 1.07 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 6.05 min following Method R. ES-MS: calcd. for $C_{20}H_{22}N_2O_3S$ (370.47) found: 371.4 [M+H].

Example 19
(*R*)-*N*-Hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide



[00282] Step 1: (*R*)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate was prepared from (*R*)-3-(*tert*-butoxycarbonyl)thiazolidine-2-carboxylic acid following Method B using the commercially available Boc-protected carboxylic acid (yield = 94%) ^{1}H NMR (DMSO-d_6): 5.43 – 5.37 (d, 1H), 3.96 (bs, 2H), 3.87 (s, 2H), 3.27 (bs, 2H), 1.59 –1.53 (d, 9H).

HPLC: Rt = 5.31 min following Method R. ES-MS: calcd. for $C_{10}H_{17}NO_4S$ (247.09); found: 269.9 [M+Na].

[00283] Step 2: (*R*)-methyl thiazolidine-2-carboxylate hydrochloride salt was prepared from (R)-3-*tert*-butyl 2-methyl thiazolidine-2,3-dicarboxylate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 5.66 (s, 1H), 3.95 (s, 3H), 3.74 – 3.70 (t, J = 6.59 & 6.32 Hz, 2H), 3.39 – 3.37 (m, 2H). ES-MS: calcd. for $C_5H_9NO_2S$ (147.2); found: 148.1[M+H].

[00284] Step 3: (*R*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate was prepared from (R)-methyl thiazolidine-2-carboxylate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 92%) ^{1}H NMR (DMSO-d_6): 8.24 – 8.17 (m, 2H), 7.98 – 7.80 (m, 4H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 5.77 (bs, 1H), 4.2 (bs, 1H), 4.09 – 4.01 (m, 1H), 3.9 (s, 3H), 3.37 – 3.33 (t, J = 6.04 & 6.32 Hz, 2H), 2.81 – 2.76 (t, J = 7.97 & 7.42 Hz, 2H), 1.87 – 1.74 (m, 2H), 1.12 – 1.07 (m, 3H). HPLC: Rt = 7.16 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_3S$ (369.48) found: 370 [M+H].

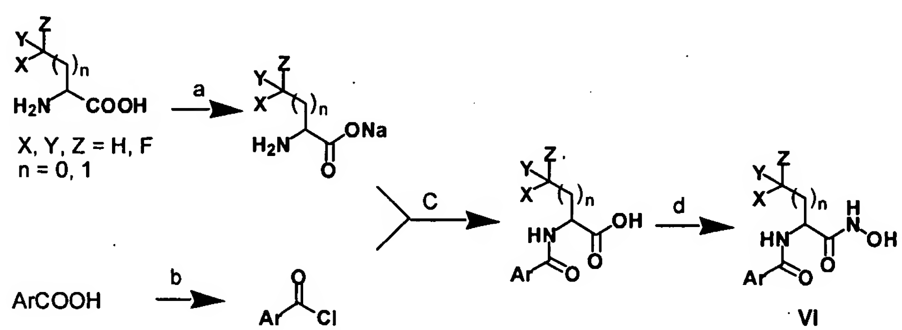
[00285] Step 4: (*R*)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxylate was prepared from (R)-methyl 3-(4'-propylbiphenylcarbonyl)thiazolidine-2-carboxylate following Method S (yield = 30%). ^{1}H NMR (DMSO-d_6): 7.99 – 7.96 (d, J = 8.24 Hz, 2H), 7.84 – 7.82 (d, J = 7.97 Hz, 4H), 7.52 – 7.49 (d, J = 7.97 Hz, 2H), 5.78 (bs, 1H), 4.34 – 4.2 (m, 2H), 4.04 – 3.95 (m, 1H), 3.99 – 3.98 (d, 3H), 3.87 – 3.58 (m, 1H), 2.81 – 2.76 (t, J =

7.42 & 7.69 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.12 – 1.07 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 6.87 min following Method R. ES-MS: calcd. for $C_{21}H_{23}NO_5S$ (401.48) found: 424.2 [M+Na].

[00286] Step 5: (*R*)-*N*-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide was prepared from (*R*)-methyl 3-(4'-propylbiphenylcarbonyl) thiazolidinesulfone-2-carboxylate following Method I (yield = 31%). HPLC: Rt = 6.90 min following Method R. ES-MS: calcd. for $C_{27}H_{28}N_2O_5S$ (492.59) found: 491.2 [M-H].

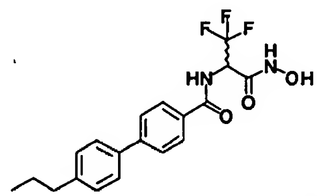
[00287] Step 6: (R)-N-hydroxy-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide was prepared from (*R*)-*N*-(benzyloxy)-3-(4'-propylbiphenylcarbonyl)thiazolidinesulfone-2-carboxamide following Method P (yield = 25%). The compound was isolated as containing ~50% of the opp0site isomer as analyzed by HPLC using a chiral column. ^{1}H NMR (DMSO-d_6): 11.27 (bs, 1H), 9.46 (bs, 1H), 7.78 – 7.75 (d, J = 8.24 Hz, 2H), 7.65 – 7.62 (d, J = 7.97 Hz, 4H), 7.32 – 7.3 (d, J = 7.97 Hz, 2H), 5.3 (bs, 1H), 4.06 (bs, 2H), 3.72 (bs, 1H), 3.52 – 3.45 (m, 3H), 2.62 – 2.57 (t, J = 7.14 & 7.69 Hz, 2H), 1.68 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.42 Hz, 3H). HPLC: Rt = 5.897 min following Method R. ES-MS: calcd. for $C_{20}H_{22}N_2O_5S$ (402.47) found: 425.3 [M+Na].

General procedure for preparation of N-Aroyl trifluoroalanine hydroxamate derivatives



[00288] Scheme I: Reagents and conditons: (a) 1N NaOH; (b) $(COCl)_2$, DMF (cat), DCM, 0 °C; (c) THF; (d) 1. $TMSCHN_2$, MeOH, 0 °C to rt, 2. NH_2OH, MeOH

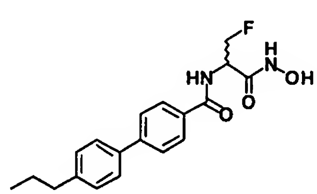
Example 20
DL-4'-Propyl-biphenyl-4-carboxylic acid (2,2,2-trifluoro-1-hydroxycarbamoyl-ethyl)-amide



[00289] Step 1: DL-3,3,3-Trifluoro-2-[(4'-propyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester is prepared from 3,3,3-trifluoro-D,L-alanine and 4-(4-n-propylphenyl)benzoic acid following Method FF (yield = 86%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.09-7.86 (m, 2H), 7.69-7.63 (m, 2H), 7.53-7.51 (m, 2H), 7.28-7.25 (m, 2H), 6.87 (d, J = 9.00 Hz, 1H), 5.62-5.56 (m, 1H), 3.89 (s, 3H), 2,62 (t, J = 6.00 Hz, 2H), 1.72-1.60 (m, 2H), 0.95 (t, J = 9.00 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$); -70.87, -73.80.

[00290] Step 2: DL-4'-Propyl-biphenyl-4-carboxylic acid (2,2,2-trifluoro-1-hydroxycarbamoyl-ethyl)-amide is prepared from DL-3,3,3-Trifluoro-2-[(4'-propyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester following Method GG (yield = 56%). ^{1}H NMR (300 MHz, DMSO-d_6):11.27 (s, 1H), 9.37 (s, 1H), 9.32 (d, J = 9.00 Hz, 1H), 8.02 (d, J = 9.00 Hz, 2H), 7.75 (d, J = 6.00 Hz, 2H), 7.64 (d, J = 9.00 Hz, 2H), 7.30 (d, J = 9.00 Hz, 2H), 5.47-5.41 (m, 1H), 2.62-2.57 (m, 2H), 1.65-1.57 (m, 2H), 0.90 (t, J = 9.00 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6); -72.50. ESMS: m/z 379 $[M-1]^-$. HPLC Rt: 6.42 min following Method R.

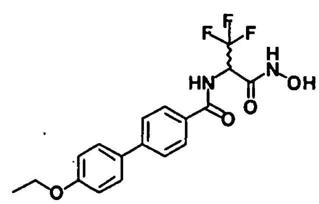
Example 21
DL-4'-Propyl-biphenyl-4-carboxylic acid (2-fluoro-1-hydroxycarbamoyl-ethyl)-amide



[00291] Step 1: DL-3-Fluoro-2-[(4'-propyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester is prepared from 3-fluoro-D,L-alanine and 4-(4-n-propylphenyl)benzoic acid following Method FF (yield = 82%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.90-7.87 (m, 2H), 7.70-7.62 (m, 2H), 7.54-7.51 (m, 2H), 7.27-7.24 (m, 2H), 5.10-4.68 (m, 2H), 4.21-4.18 (m, 1H), 3.91-3.85 (m, 3H), 2.62 (t, J = 9.00 Hz, 2H), 1.72-1.60 (m, 2H), 0.98-0.84 (m, 3H). ^{19}F NMR (282 MHz, $CDCl_3$):-52.77- -53.22 (m).

[00292] Step 2: DL-4'-Propyl-biphenyl-4-carboxylic acid (2-fluoro-1-hydroxycarbamoyl-ethyl)-amide is prepared from DL-3-Fluoro-2-[(4'-propyl-biphenyl-4-carbonyl)-amino]-propionic acid methyl ester following Method FF (yield = 42%). ^{1}H NMR (300 MHz, DMSO-d_6): 10.90 (s, 1H), 9.00 (s, 1H), 8.76 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 9.00 Hz, 2H), 7.75 (d, J = 8.10 Hz, 2H), 7.64 (d, J = 8.10 Hz, 2H), 7.29 (d, J = 9.00 Hz, 2H), 4.82-4.57 (m, 3H), 2.62-2.56 (m, 2H), 1.65-1.57 (m, 2H), 0.90 (t, J = 7.20 Hz, 3H). ^{19}F NMR (282 MHz, DMSO): -73.77. ESMS: m/z 343 $[M-1]^-$. HPLC Rt: 5.97 min following Method R.

Example 22
DL-4'-Ethoxy-biphenyl-4-carboxylic acid (2,2,2-trifluoro-1-hydroxycarbamoyl-ethyl)-amide

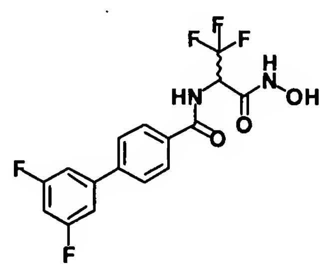


[00293] Step 1: DL-2-[(4'-Ethoxy-biphenyl-4-carbonyl)-amino]-3,3,3-trifluoro-propionic acid methyl ester is prepared from 3,3,3-trifluoro-D,L-alanine and 4-ethoxy-4'-biphenylcarboxylic acid following Method FF (yield = 92%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.88-7.85 (m, 2H), 7.65-7.62 (m, 2H), 7.55-7.51 (m, 2H), 6.98-6.95 (m, 2H), 6.83 (d, J = 9.00 Hz, 1H), 5.63-5.53 (m, 1H), 4.10-4.03 (m, 2H), 3.88 (s, 3H), 1.43 (t, J = 7.20 Hz, 3H).). ^{19}F NMR (282 MHz, $CDCl_3$): -72.54.

[00294] Step 2: DL-4'-Ethoxy-biphenyl-4-carboxylic acid (2,2,2-trifluoro-1-hydroxycarbamoyl-ethyl)-amide is prepared from DL-2-[(4'-Ethoxy-biphenyl-4-carbonyl)-amino]-3,3,3-trifluoro-propionic acid methyl ester following Method GG (yield = 46%). ^{1}H NMR (300 MHz, DMSO-d_6):11.27 (s, 1H), 9.37 (s, 1H), 9.27 (d, J = 9.00 Hz, 1H), 7.99 (d, J = 9.00 Hz, 2H), 7.73-7.66 (m, 4H), 7.02 (d, j = 9.00 Hz, 1H), 5.44 (t, J = 9.00 Hz, 1H), 4.10-4.03 (m, 2H), 1.34 (t, J = 6.00 Hz, 3H). ^{19}F NMR (282 MHz, DMSO-d_6) ; -70.89, -73.76. ESMS: m/z 381 [M-1]. HPLC Rt: 5.25 min following Method R.

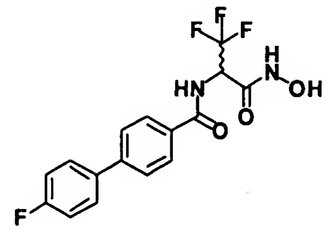
Example 23

DL-3',5'-Difluoro-biphenyl-4-carboxylic acid (2,2,2-trifluoro-1-hydroxycarbamoyl-ethyl)-amide



[00295] Step 1: DL-2-[(3',5'-Difluoro-biphenyl-4-carbonyl)-amino]-3,3,3-trifluoro-propionic acid methyl ester is prepared from 3,3,3-trifluoro-D,L-alanine and 4-biphenyl-3',5'-difluorocarboxylic acid following Method FF I(yield = 87%). ^{1}H NMR (300 MHz, $CDCl_3$): 7.98-7.89 (m, 2H), 7.65-7.61 (m, 2H), 7.14-7.07 (m, 2H), 6.88-6.79 (m, 2H), 5.60-5.54 (m, 1H), 3.90 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$); -72.48, -109.16.

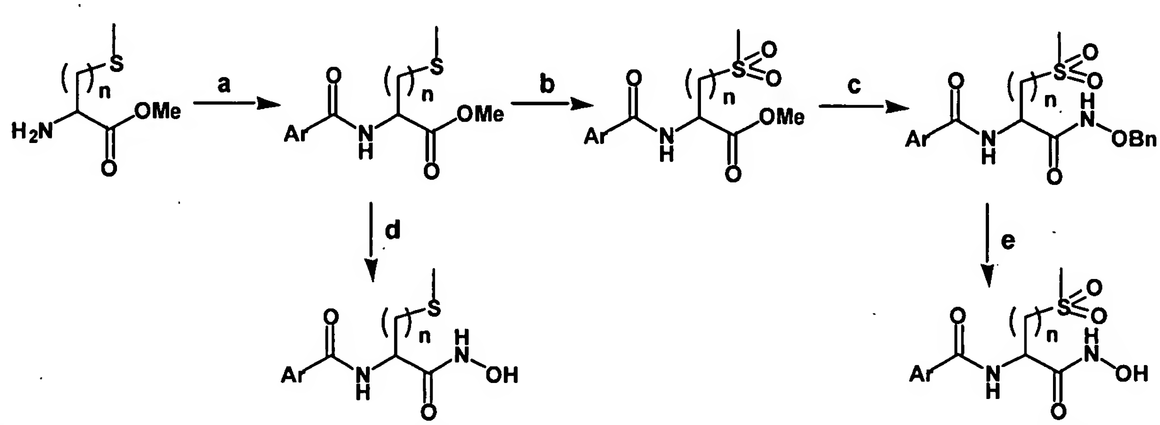
[00296] Step 2: DL-3',5'-Difluoro-biphenyl-4-carboxylic acid (2,2,2-trifluoro-1-hydroxycarbamoyl-ethyl)-amide is prepared from DL-2-[(3',5'-Difluoro-biphenyl-4-carbonyl)-amino]-3,3,3-trifluoro-propionic acid methyl ester following Method GG (yield = 48%). ^{1}H NMR (300 MHz, DMSO--d_6); 11.24 (br s, 1H), 9.44-9.38 (m, 2H), 8.04 (d, J = 9.00 Hz, 2H), 7.86 (d, J = 9.00 Hz, 2H), 7.55-7.52 (m, 2H), 7.32-7.25 (m, 1H), 5.47-5.41 (m, 1H). ^{19}F NMR



[00299] DL-methyl-3,3,3-triflurobiphenyl-4-ylcarboxamido)propanoate is prepared from 3,3,3-trifluoro-D,L-alanine and 4'-fluoro-biphenyl-4-carboxylic acid following Method FF. This material was used without any further purification.

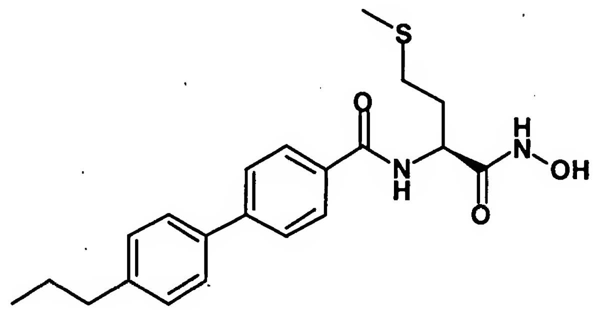
[00300] DL-4'-fluoro-N-(1,1,1-trifluoro-3-(hydroxyamino)-3-oxopropan-2-yl)biphenyl-4-carboxamide is prepared from DL-methyl-3,3,3-triflurobiphenyl-4-ylcarboxamido)propanoate following Method GG (yield = 33%). ^{1}H NMR (300 MHz, DMSO-d_6): 11.28 (s, 1H), 9.38-9.33 (m, 2H), 8.02 (d, J = 9.00 Hz, 2H), 7.81-7.75 (m, 4H), 7.35-7.29 (m, 2H), 5.47-5.41 (m, 1H). ^{19}F NMR (282 MHz, DMSO-d_6): -70.88, -73.82, -114.55. ESMS: m/z 355 [M-1]$^-$. HPLC Rt: 5.40 min following Method R.

General Synthesis of N-Aroyl 2-(Methylthio)alkyl Glycine Hydroxamates.



[00301] **Scheme J:** Reagents and conditions. (a) Coupling (ArCOOH, HATU, DIEA, DMF). (b) Oxidation (MCPBA, DCM). (c) Amidation (Me_3Al, NH_2-OBn.HCl, Toluene). (d) Hydroxamate formation (NH_2OH.HCl, NaOMe, MeOH). (e) Hydroxamate formation (10% $Pd(OH)_2$, EtOH).

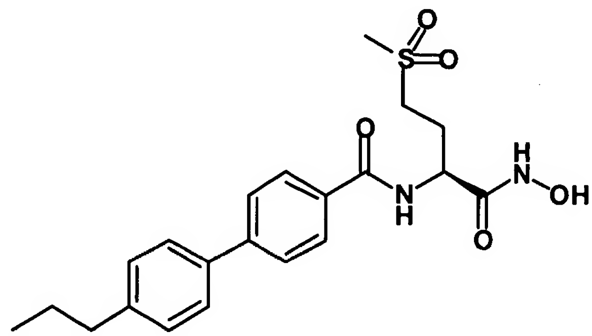
Example 26
(S)-N-(1-(Hydroxyamino)-4-(methylthio)-1-oxobutan-2-yl)-4'-propylbiphenyl-4-carboxamide



[00302] Step 1: (*S*)-methyl 4-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido)butanoate was prepared from (*S*)-methyl 2-amino-4-(methylthio)butanoate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 87%). The methyl ester was available commercially. ^{1}H NMR (DMSO-d_6): 8.81 – 8.79 (d, J = 7.42 Hz, 1H), 7.97 – 7.94 (d, J = 8.52 Hz, 2H), 7.78 – 7.75 (d, J = 8.52 Hz, 2H), 7.66 – 7.63 (d, J = 8.24 Hz, 2H), 7.32 – 7.29 (d, 8.24 Hz, 2H), 4.63 – 4.56 (dd, J = 7.97 & 7.69 Hz, 1H), 3.65 (s, 3H), 2.61 – 2.56 (t, J = 7.42 & 6.87 Hz, 4H), 2.1 – 2.03 (m, 2H), 2.06 (s, 3H), 1.67 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.18 min following Method R. ES-MS: calcd. for $C_{22}H_{27}NO_3S$ (385.17) found: 386.1 [M+H].

[00303] Step 2: (*S*)-*N*-(1-(hydroxyamino)-4-(methylthio)-1-oxobutan-2-yl)-4'-propylbiphenyl-4-carboxamide was prepared from (*S*)-methyl 4-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido)butanoate following Method H (yield = 10%) ^{1}H NMR (DMSO-d_6): 10.92 (s, 1H), 9.04 (s, 1H), 8.75 – 8.72 (d, J = 7.69 Hz, 1H), 8.17 – 8.15 (d, J = 7.97 Hz, 2H), 7.95 – 7.92 (d, J = 8.24 Hz, 2H), 7.85 – 7.82 (d, J = 8.24 Hz, 2H), 7.51 – 7.48 (d, 8.24 Hz, 2H), 4.67 – 4.62 (m, 1H), 3.42 – 2.74 (m, 4H), 2.25 (s, 3H), 2.2 – 2.15 (t, 6.04 – 8.24 Hz, 1.86 - 1.77 (m, 2H), 1.13 – 1.08 (t, J = 7.42 Hz, 3H). HPLC: Rt = 6.26 min following Method R. ES-MS: calcd. for $C_{21}H_{26}N_2O_3S$ (386.51) found: 409.2 [M+Na].

Example 27
(*S*)-*N*-(1-(Hydroxyamino)-4-(methylsulfone)-1-oxobutan-2-yl)-4'-propylbiphenyl-4-carboxamide



[00304] Step 1: (*S*)-methyl 4-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido)butanoate was prepared from (*S*)-methyl 2-amino-4-(methylthio)butanoate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 87%) ^{1}H NMR (DMSO-d_6): 8.81 – 8.79 (d, J = 7.42 Hz, 1H), 7.97 – 7.94 (d, J = 8.52 Hz, 2H), 7.78 – 7.75 (d, J = 8.52 Hz, 2H), 7.66 – 7.63 (d, J = 8.24 Hz, 2H), 7.32 – 7.29 (d, 8.24 Hz, 2H), 4.63 – 4.56 (dd, J = 7.97 & 7.69 Hz, 1H), 3.65 (s, 3H), 2.61 – 2.56 (t, J = 7.42 & 6.87 Hz, 4H), 2.1 – 2.03 (m, 2H), 2.06 (s, 3H), 1.67 – 1.55 (m, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.18 min following Method R. ES-MS: calcd. for $C_{22}H_{27}NO_3S$ (385.17) found: 386.1 [M+H].

[00305] Step 2: (*S*)-methyl 4-(methylsulfone)-2-(4'-propylbiphenyl-4-ylcarboxamido)butanoate was prepared from (*S*)-methyl 4-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido) butanoate following Method S (yield = 75%). ^{1}H NMR (DMSO-d_6): 9.1 – 9.08 (d, J = 7.69 Hz, 1H), 8.2 – 8.17 (d, J = 8.52 Hz, 2H), 7.97 – 7.94 (d, J = 8.24 Hz, 2H), 7.86 – 7.83 (d, J = 7.97 Hz, 2H), 7.51 – 7.5 (d, 7.69 Hz, 2H), 4.82 – 4.81 (m, 1H), 3.87 (s, 3H), 3.51 – 3.43 (m, 2H), 3.2 (s, 3H), 2.81 – 2.77 (t, J = 7.42 & 7.14 Hz, 2H), 2.47 – 2.41 (m, 2H), 1.85 – 1.77 (m, 2H), 1.13 – 1.08 (t, J = 7.42 Hz, 3H). HPLC: Rt = 6.49 min following Method R. ES-MS: calcd. for $C_{22}H_{27}NO_5S$ (417.52) found: 418.3 [M+H].

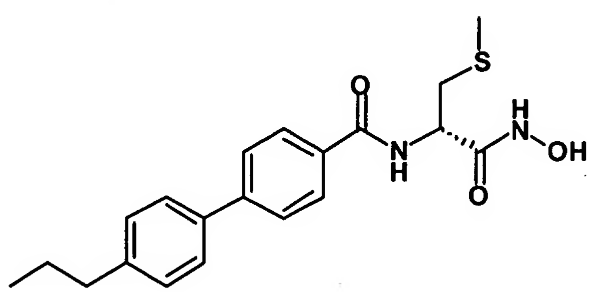
[00306] Step 3: (*S*)-*N*-(1-(benzyloxyamino)-4-(methylsulfone)-1-oxobutan-2-yl)-4'-propylbiphenyl-4-carboxamide was prepared from (*S*)-methyl 4-(methylsulfone)-2-(4'-propylbiphenyl-4-ylcarboxamido)butanoate following Method I (yield = 61%). ^{1}H NMR

(DMSO-d_6): 11.59 (s, 1H), 8.89 – 8.86 (d, J = 7.69 Hz, 1H), 8.17 – 8.15 (d, J = 8.24 Hz, 2H), 7.98 – 7.95 (d, J = 7.97 Hz, 2H), 7.85 – 7.83 (d, J = 7.97 Hz, 2H), 7.6 – 7.5 (d, 7.69 Hz, 7H), 5 (bs, 2H), 4.66 –4.64 (m, 1H), 3.36 – 3.31 (t, J = 7.14 & 8.79 Hz, 2H), 3.2 (bs, 3H), 2.81 – 2.76 (t, J = 7.14 & 7.69 Hz, 2H), 2.35 – 2.33 (m, 2H), 1.85 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 Hz, 3H). HPLC: Rt = 6.69 min following Method R. ES-MS: calcd. for $C_{28}H_{32}N_2O_5S$ (508.63) found: 509.3 [M+H].

[00307] Step 4: (*S*)-*N*-(1-(hydroxyamino)-4-(methylsulfone)-1-oxobutan-2-yl)-4'-propylbiphenyl-4-carboxamide was prepared from (*S*)-*N*-(1-(benzyloxyamino)-4-(methylsulfone)-1-oxobutan-2-yl)-4'-propylbiphenyl-4-carboxamide following Method P (yield =15%). ^{1}H NMR (DMSO-d_6): 10.98 (s, 1H), 9.12 (s, 1H), 8.84 – 8.82 (d, J = 7.97 Hz, 1H), 8.19 – 8.16 (d, J = 8.24 Hz, 2H), 7.96 – 7.94 (d, J = 8.24 Hz, 2H), 7.86 – 7.83 (d, J = 8.24 Hz, 2H), 7.51 – 7.49 (d, 7.97 Hz, 2H), 4.72 – 4.64 (dd, J = 7.97 & 7.42 Hz, 1H), 3.37 – 3.32 (t, J = 7.97 Hz, 2H), 3.2 (bs, 3H), 2.82 – 2.73 (m, 2H), 2.35 – 2.26 (m, 2H), 1.85 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 5.827 min following Method R. ES-MS: calcd. for $C_{21}H_{26}N_2O_5S$ (418.51) found: 417.2 [M-H].

Example 28

(*S*)-N-(1-(Hydroxyamino)-3-(methylthio)-1-oxopropan-2-yl)-4'-propylbiphenyl-4-carboxamide



[00308] Step 1: (*S*)-methyl 2-(3,3-dimethylbutanamido)-3-(methylthio)propanoate was prepared from (*S*)-2-(3,3-dimethylbutanamido)-3-(methylthio)propanoic acid following Method B (yield = 78%-80%). ^{1}H NMR (DMSO-d_6): 7.31 – 7.28 (d, J = 8.24 Hz, 1H) 4.18 – 4.11 (dd, J = 7.97 & 8.24 Hz, 1H), 3.63 (s, 3H), 2.83 – 2.50 (m, 2H), 2.1 – 2.05 (d, J = 1.37 Hz, 3H), 1.37 (s,

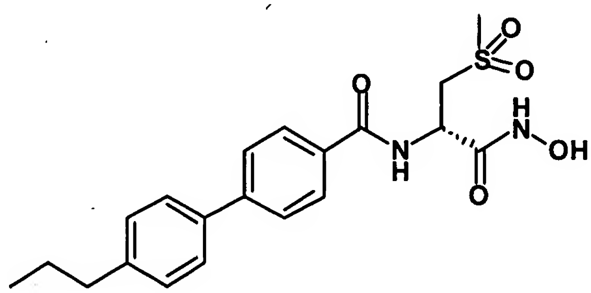
9H). HPLC: Rt = 5 min following Method R. ES-MS: calcd. for $C_{10}H_{19}NO_4S$ (249.1) found: 272 [M+Na].

[00309] Step 2: (*S*)-methyl 2-amino-3-(methylthio)propanoate hydrochloride salt was prepared from (*S*)-methyl 2-(3,3-dimethylbutanamido)-3-(methylthio)propanoate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 8.79 (bs, 2H) 4.29 – 4.25 (t, J = 5.77 Hz, 1H), 3.75 (s, 3H), 3.03 – 3.01 (d, J = 5.77 Hz, 2H), 2.1 (s, 3H). ES-MS: calcd. for $C_5H_{11}NO_2S$ (149.05) found: 150.2 [M+H].

[00310] Step 3: (*S*)-methyl 3-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoate was prepared from (*S*)-methyl 2-amino-3-(methylthio)propanoate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 78%-80%). ^{1}H NMR (DMSO-d_6): 9.11 – 9.08 (d, J = 7.97 Hz, 1H), 8.16 – 8.14 (d, J = 7.69 Hz, 2H), 7.98 – 7.96 (d, J = 8.52 Hz, 2H), 7.86 – 7.83 (d, J = 7.69 Hz, 2H), 7.51 – 7.49 (d, 7.69 Hz, 2H), 4.9 – 4.82 (m, 1H), 3.86 (s, 3H), 3.2 –3.08 (m, 2H), 2.82 – 2.76 (t, J = 7.69 & 7.42 Hz, 2H), 2.29 (s, 3H), 1.85 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.12 min following Method R. ES-MS: calcd. for $C_{21}H_{25}NO_3S$ (371.16) found: 394.1 [M+Na].

[00311] Step 4: (*S*)-N-(1-(hydroxyamino)-3-(methylthio)-1-oxopropan-2-yl)-4'-propylbiphenyl-4-carboxamide was prepared from (*S*)-methyl 3-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoate following Method H (yield = 20%). ^{1}H NMR (DMSO-d_6): 11.05 (bs, 1H), 9.14 – 9.13 (d, J = 1.1 Hz, 1H), 8.83 – 8.80 (d, J = 8.52 Hz, 1H), 8.17 – 8.15 (d, J = 8.24 Hz, 2H), 7.96 – 7.93 (d, J = 8.52 Hz, 2H), 7.8 – 7.82 (d, 8.24 Hz, 2H), 7.51 – 7.48 (d, J = 7.97 Hz, 2H), 4.81 – 4.73 (dd, J = 7.97 Hz, 1H), 3.05 –3.02 (m, 2H), 2.81 – 2.76 (t, J = 7.42 & 7.69 Hz, 2H), 2.28 (s, 3H), 1.87 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 6.19 min following Method R. ES-MS: calcd. for $C_{20}H_{24}N_2O_3S$ (372.49) found: 395.2 [M+Na].

Example 29
(S)-N-(1-(Hydroxyamino)-3-(methylsulfone)-1-oxopropan-2-yl)-4'-propylbiphenyl-4-carboxamide



[00312] Step 1: (*S*)-methyl 2-(3,3-dimethylbutanamido)-3-(methylthio)propanoate was prepared from (*S*)-2-(3,3-dimethylbutanamido)-3-(methylthio)propanoic acid following Method B (yield = 78%-80%). ^{1}H NMR (DMSO-d_6): 7.31 – 7.28 (d, J = 8.24 Hz, 1H) 4.18 – 4.11 (dd, J = 7.97 & 8.24 Hz, 1H), 3.63 (s, 3H), 2.83 – 2.50 (m, 2H), 2.1 – 2.05 (d, J = 1.37 Hz, 3H), 1.37 (s, 9H).

[00313] Step 2: (*S*)-methyl 2-amino-3-(methylthio)propanoate hydrochloride salt was prepared from (*S*)-methyl 2-(3,3-dimethylbutanamido)-3-(methylthio)propanoate following Method F (quantitative yield). ^{1}H NMR (DMSO-d_6): 8.79 (bs, 2H) 4.29 – 4.25 (t, J = 5.77 Hz, 1H), 3.75 (s, 3H), 3.03 – 3.01 (d, J = 5.77 Hz, 2H), 2.1 (s, 3H). ES-MS: calcd. for $C_5H_{11}NO_2S$ (149.05) found: 150.2 [M+H].

[00314] Step 3: (*S*)-methyl 3-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoate was prepared from (*S*)-methyl 2-amino-3-(methylthio)propanoate hydrochloride salt and 4-(p-n-propylphenyl)-benzoic acid following Method G (yield = 78%-80%) ^{1}H NMR (DMSO-d_6): 9.11 – 9.08 (d, J = 7.97 Hz, 1H), 8.16 – 8.14 (d, J = 7.69 Hz, 2H), 7.98 – 7.96 (d, J = 8.52 Hz, 2H), 7.86 – 7.83 (d, J = 7.69 Hz, 2H), 7.51 – 7.49 (d, 7.69 Hz, 2H), 4.9 – 4.82 (m, 1H), 3.86 (s, 3H), 3.2 –3.08 (m, 2H), 2.82 – 2.76 (t, J = 7.69 & 7.42 Hz, 4H), 2.29 (s, 3H), 1.85 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 7.12 min following Method R. ES-MS: calcd. for $C_{21}H_{25}NO_3S$ (371.16) found: s394.1 [M+Na].

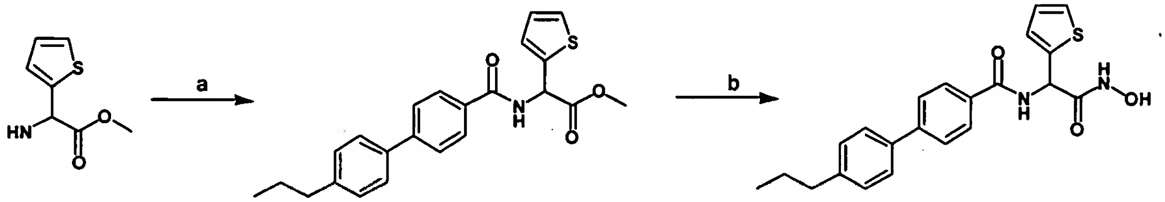
[00315] Step 3: (*S*)-methyl 3-(methylsulfone)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoate was prepared from *S*)-methyl 3-(methylthio)-2-(4'-propylbiphenyl-4-ylcarboxamido) propanoate following Method S (yield = 46%). ^{1}H NMR (DMSO-d_6): 9.39 – 9.37 (d, J = 7.97 Hz, 1H), 8.14 – 8.12 (d, J = 8.24 Hz, 2H), 7.99 – 7.96 (d, J = 8.24 Hz, 2H), 7.86 – 7.83 (d, J = 7.97 Hz, 2H), 7.52 – 7.49 (d, 8.24 Hz, 2H), 5.16 – 5.09 (dd, J = 7.14 & 6.59 Hz, 1H), 3.94 – 3.92 (d, J = 6.59 Hz, 2H), 3.88 (s, 3H), 3.25 (s, 3H), 2.81 – 2.76 (t, J = 7.42 & 7.69 Hz, 2H), 1.87 – 1.75 (m, 2H), 1.13 – 1.08 (t, J = 7.42 Hz, 3H). HPLC: Rt = 6.44 min following Method R. ES-MS: calcd. for $C_{21}H_{25}NO_5S$ (403.15) found: 404.3 [M+H].

[00316] Step 5: (S)-N-(1-(benzyloxyamino)-3-(methylsulfone)-1-oxopropan-2-yl)-4'-propylbiphenyl-4-carboxamide was prepared from (*S*)-methyl 3-(methylsulfone)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoate following Method I (yield = 55%). ^{1}H NMR (DMSO-d_6): 11.6 (bs, 1H), 8.94 – 8.92 (d, J = 8.52 Hz, 1H), 7.97 – 7.95 (d, J = 8.24 Hz, 2H), 7.79 – 7.76 (d, J = 8.24 Hz, 2H), 7.67 – 7.64 (d, J = 7.97 Hz, 2H), 7.4 – 7.3 (m, 7H), 4.92 – 4.91 (m, 1H), 4.79 (bs, 2H), 3.65 – 3.59 (m, 1H), 3.32 (bs, 1H), 3.02 (s, 3H), 2.62 – 2.57 (t, J = 7.14 & 7.69 Hz, 2H), 1.65 – 1.58 (m, 2H), 0.93 – 0.88 (t, J = 7.42 & 7.14 Hz, 3H). HPLC: Rt = 6.8 min following Method R. ES-MS: calcd. for $C_{27}H_{30}N_2O_5S$ (494.16) found: 493.2 [M-H].

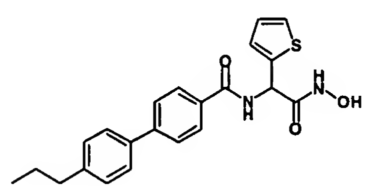
[00317] Step 6: (*S*)-N-(1-(hydroxyamino)-3-(methylsulfone)-1-oxopropan-2-yl)-4'-propylbiphenyl-4-carboxamide was prepared from (S)-N-(1-(benzyloxyamino)-3-(methylsulfone)-1-oxopropan-2-yl)-4'-propylbiphenyl-4-carboxamide following Method P (yield = 20%). ^{1}H NMR (DMSO-d_6): 10.95 (bs, 1H), 9.01 (bs, 1H), 8.89 – 8.86 (d, J = 8.52 Hz, 1H), 7.97 – 7.94 (d, J = 8.24 Hz, 2H), 7.78 – 7.75 (d, J = 8.52 Hz, 2H), 7.66 – 7.63 (d, J = 8.24 Hz, 2H), 7.32 – 7.3 (d, J = 7.97 Hz, 2H), 4.94 (bs, 1H), 3.71 – 3.55 (m, 2H), 3.02 (s, 3H), 2.62 – 2.57 (t, J = 7.14 & 7.97 Hz, 2H), 1.65 – 1.58 (dd, J = 7.14 Hz, 2H), 0.93 – 0.88 (t, J = 7.14 & 7.42 Hz, 3H). HPLC: Rt = 5.804 min following Method R. ES-MS: calcd. for $C_{20}H_{24}N_2O_5S$ (404.485) found: 403.2 [M-H].

Synthesis of 2-Heteroaryl- and 2-Heteroarylalkyl Glycine Hydroxamate Derivatives.

Example 30
N-(2-(Hydroxyamino)-2-oxo-1-(thiophen-2-yl)ethyl)-4'-propylbiphenyl-4-carboxamide



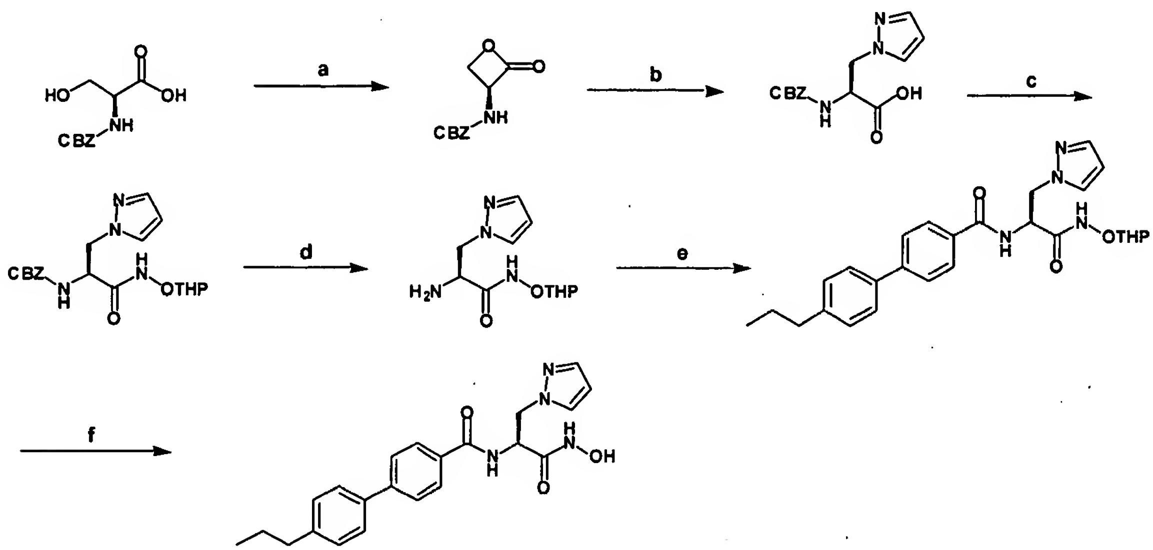
[00318] **Scheme K** : Reagents and conditions. (a) 4-(4-n-propylphenyl)benzoic acid, HATU, DIEA, DMF, rt, 18 h; (b) hydroxylamine hydrochloride, MeOH, NaOMe, rt, 2 h.



[00319] Step 1: Methyl 2-(4'-propylbiphenyl-4-ylcarboxamido)-2-(thiophen-2-yl)acetate is prepared from 4-(4-propylphenyl)benzoic acid and methyl 2-amino-2-(thiophen-2-yl)acetate following Method G (yield = 34%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 7.89 (d, J = 9.0 Hz, 2 H), 7.66 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2 H), 7.32-7.23 (m, 3 H), 7.17-7.06 (m, 2 H), 7.00 (dd, J = 5.4, 3.6 Hz, 1 H), 3.89 (s, 3 H), 2.64 (t, J = 7.2 Hz, 2H), 1.74-1.61 (m, 2 H), 0.97 (t, J = 6.9 Hz, 3 H).

[00320] Step 2: *N*-(2-(hydroxyamino)-2-oxo-1-(thiophen-2-yl)ethyl)-4'-propylbiphenyl-4-carboxamide is prepared from methyl 2-(4'-propylbiphenyl-4-ylcarboxamido)-2-(thiophen-2-yl)acetate following Method H (yield = 9%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.03 (s, 1 H), 9.19-8.99 (m, 2 H), 8.00 (d, J = 8.4 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2 H), 7.47 (d, J = 5.1 Hz, 1 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.15 (d, J = 3.3 Hz, 1 H), 7.00 (dd, J = 5.1, 3.3 Hz, 1 H), 5.86 (d, J = 8.1 Hz, 1 H), 2.63-2.42 (m, 3 H), 1.69-1.55 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H); ESI(+) calcd. for $C_{22}H_{23}N_2O_3S$ (305.14), found 395.5.

Example 31
(*S*)-3-(1*H*-Imidazol-1-yl)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoic acid



[00321] Scheme L: Reagents and conditions. (a) DIAD, Ph_3P, THF, -78 °C, 3h 50 min; (b) pyrazole, ACN, 55°C, 24 h; (c) HATU, DIEA, DMF, O-(tetrahydro-2H-pyran-2-yl)hydroxylamine, rt, 18 h; (d) 10% Pd/C, EtOH, H_2, rt, 8 h; (e) 4-(4-n-propylphenyl)benzoic acid, HATU, DIEA, DMF, rt, 18 h (f) TFA, DCM, rt, 2 h.

[00322] Step 1: (Steps 1 and 2 are done similar to that described in Organic Syntheses, Coll. Vol. 9, p.58 – 63) To a solution of triphenylphosphine (27.7 g, 106 mmol) in THF (500 mL) at –78°C, DIAD (20.8 mL, 106 mmol) was added dropwise. The mixture is stirred at –78°C for 20 min. A solution of *N*-(benzyloxycarbonyl)-*L*-serine (25.3 g, 106 mmol) in THF (150 mL) is added to the reaction mixture. The reaction mixture is stirred for an additional 30 min at –78°C, warmed to rt, and stirred for an additional 3 h. The reaction mixture is concentrated *in vacuo*, dissolved in ether, and filtered. The filtrate was concentrated *in vacuo*, and the residue is purified by column chromatography (SiO_2, gradient 10%-40% ethyl acetate in hexanes). This gave 8.0 g of *N*-(benzyloxycarbonyl)-*L*-serine β-lactone. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73-7.43 (m, 5 H), 5.80-5.66 (m, 1 H), 5.48-5.28 (m, 3 H), 4.77-4.69 (m, 2 H).

[00323] Step 2: *N*-(Benzyloxycarbonyl)-*L*-serine *β*-lactone (1.5 g, 6.8 mmol), pyrazole (0.49 g, 7.2 mmol), and acetonitrile (25 mL) are combined and stirred for 12 h at 55°C. An additional charge of pyrazole (0.25 g, 3.6 mmol) is added to the reaction and stirred for an additional 12 h. The reaction mixture is concentrated *in vacuo*. The residue is dissolved in sodium hydroxide solution (1 M), and washed with DCM. The aqueous solution was neutralized with HCl solution (1 M) to precipitate *N*-(benzyloxycarbonyl)-*β*-(pyrazol-1-yl)-*L*-alanine (1.1 g). The compound is used in the next reaction without further purification.

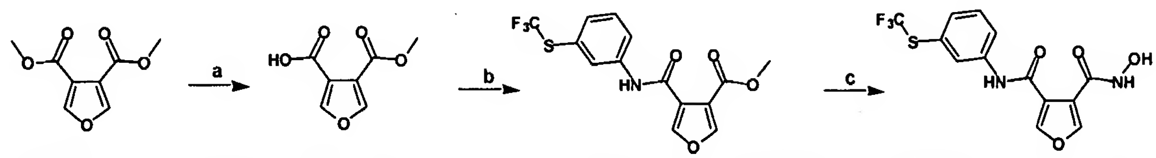
[00324] Step 3: (2*S*)-Tetrahydro-2*H*-pyran-2-yl 2-(benzyloxycarbonylamino)-3-(1*H*-imidazol-1-yl)propanoate is prepared from *N*-(benzyloxycarbonyl)-*β*-(pyrazol-1-yl)-*L*-alanine and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine following Method G. ESI(+) calcd. for $C_{19}H_{25}N_4O_5$ (389.18), found 389.2.

[00325] Step 4: (2*S*)-Tetrahydro-2*H*-pyran-2-yl 2-amino-3-(1*H*-imidazol-1-yl)propanoate is prepared from (2*S*)-tetrahydro-2*H*-pyran-2-yl 2-(benzyloxycarbonylamino)-3-(1*H*-imidazol-1-yl)propanoate following Method Z. ESI(-) calcd. for $C_{11}H_{17}N_4O_3$ (253.13), found 253.2.

[00326] Step 5: (2*S*)-Tetrahydro-2*H*-pyran-2-yl 3-(1*H*-imidazol-1-yl)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoate is prepared from (2*S*)-tetrahydro-2*H*-pyran-2-yl 2-amino-3-(1*H*-imidazol-1-yl)propanoate and 4-(4-propylphenyl)benzoic acid following Method G. ESI(+) calcd. for $C_{27}H_{33}N_4O_4$ (477.25), found 477.1.

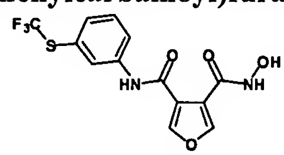
[00327] Step 6: (*S*)-3-(1*H*-Imidazol-1-yl)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoic acid is prepared from (2*S*)-tetrahydro-2*H*-pyran-2-yl 3-(1*H*-imidazol-1-yl)-2-(4'-propylbiphenyl-4-ylcarboxamido)propanoate following Method AA. The compound is dissolved in DMSO, and purified by preparative-HPLC (yield - 6%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.98 (s, 1 H), 9.14-8.62 (m, 1 H), 8.17-7.20 (m, 11 H), 6.34-6.09 (m, 1 H), 5.00-

4.33 (m, 3 H), 2.75-2.36 (m, 2 H), 1.81-1.39 (m, 2 H), 1.02-0.73 (m, 3 H) ;ESI(+) calcd. for $C_{22}H_{25}N_4O_3$ (393.19), found 393.1.



[00328] Scheme M : Reagents and conditions. (a) NaOH water, MeOH, 4°C, 18 h; (b) HATU, DIEA, DMF, 3-(trifluoromethylthio) aniline, rt, 18 h; (c) hydroxylamine hydrochloride, MeOH, NaOMe, rt, 2 h.

Example 32
Methyl 4-(3-(trifluoromethylthio)phenylcarbamoyl)furan-3-carboxylate



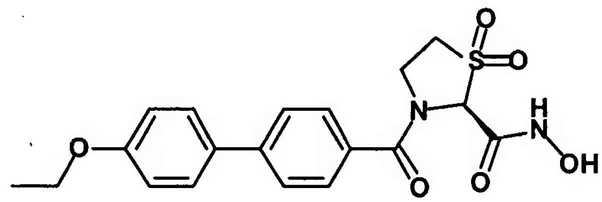
[00329] Step 1: 4-(Methoxycarbonyl)furan-3-carboxylic acid is prepared from dimethyl furan-3,4-dicarboxylate following Method BB (yield = 50%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40-8.28 (m, 2 H), 3.78 (s, 3 H).

[00330] Step 2: Methyl 4-(3-(trifluoromethylthio)phenylcarbamoyl)furan-3-carboxylate is prepared from 4-(methoxycarbonyl)furan-3-carboxylic acid and 3-(trifluoromethylthio) aniline following Method G (yield = 78%). ^{1}H NMR (300 MHz, $CHCl_3$) δ 11.66 (s, 1 H), 8.29 (s, 1 H), 8.22-8.09 (m, 1 H), 7.96-7.82 (m, 2 H), 7.50-7.37 (m, 2 H), 3.99 (s, 3 H); ESI(-) calcd. for C14H9F3NO4S (344.02), found 344.0.

[00331] Step 3: Methyl 4-(3-(trifluoromethylthio)phenylcarbamoyl)furan-3-carboxylate is prepared from N3-hydroxy-N4-(3-(trifluoromethylthio)phenyl)furan-3,4-dicarboxamide following Method H. The compound was purified by preparative-HPLC (yield = 18%). 1H

NMR (300 MHz, DMSO-d_6) δ 12.22 (s, 1 H), 11.61 (s, 1 H), 9.54 (s, 1 H), 8.47 (s, 1 H), 8.28 (s, 1 H), 8.13 (s, 1 H), 7.84-7.39 (m, 3 H); ESI(-) calcd. for $C_{13}H_8F_3N_2O_4S$ (345.02), found 345.0.

Example 33
(*S*)-3-(4′-Ethoxybiphenylcarbonyl)-*N*-hydroxythiazolidinesulfone-2-carboxamide



[00332] Step 1: (*S*)-(*tert*-butoxycarbonyl)thiazolidine-2-carboxylic acid was prepared following Method A using the commercially available (*S*)-2-thiazolidinecarboxylic acid (yield = 96%). ^{1}H NMR (DMSO-d_6): 5.29 – 5.22 (bs, 1H), 4.52 (bs, 2H), 3.64 – 3.52 (m, 2H), 1.55 (bs, 9H). ES-MS: calcd. for $C_9H_{15}NO_4S$ (233.07); found: 256.2 [M+Na]..

[00333] Step 2: *S*)-*tert*-butyl 2-(benzyloxycarbamoyl)thiazolidine-3-carboxylate was prepared from and O-benzyl hydroxylamine following Method G (yield = 67%). ^{1}H NMR (DMSO-d_6): 11.474 (bs, 1 H), 7.6 – 7.55 (m, 5H), 4.97 (bs, 1H), 3.94 – 3.8 (m, 2H), 3.44 – 3.23 (m, 2H), 1.58 – 1.53 (m, 9H). HPLC: Rt = 5.293 min following Method R. ES-MS: calcd. for $C_{16}H_{22}N_2O_4S$ (338.13); found: 337.2 [M-H].

[00334] Step 3: (*S*)-*N*-(benzyloxy)thiazolidine-2-carboxamide hydrochloride salt was prepared from (*S*)-*tert*-butyl 2-(benzyloxycarbamoyl)thiazolidine-3-carboxylate following Method F (quantitative yield) ^{1}H NMR (DMSO-d_6): 11.91 (bs, 1H), 7.4 – 7.33 (m, 5H), 5.07 (s, 1H), 4.82 (m, 2H), 3.67 – 3.56 (m, 2H), 3.55 – 3.46 (m, 2H), 3.2 – 3.15 (m, 2H). ES-MS: calcd. for $C_{11}H_{14}N_2O_2S$ (238.08); found: 239.1 [M+H].

[00335] Step 4: (*S*)-*N*-(benzyloxy)3-(4'-ethoxybiphenylcarbonyl)-thiazolidine-2-carboxamide was prepared from (*S*)-*N*-(benzyloxy)thiazolidine-2-carboxamide hydrochloride salt and 3-(4'-ethoxybiphenyl)-carboxylic acid following Method G (yield = 48%). ^{1}H NMR

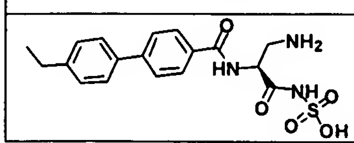
(DMSO-d_6): 11.56 (bs, 1H), 7.84 – 7.81 (d, J = 8.52 Hz, 6H), 7.58 – 7.55 (t, J = 4.67 & 5.49 Hz, 5H), 7.23 – 7.20 (d, J = 8.79 Hz, 2H), 5.67 (bs, 1H), 4.98 (s, 2H), 4.27 – 4.18 (m, 3H), 4.08 (bs, 1H), 3.45 – 3.25 (m, 2H), 1.56 – 1.51 (t, J = 7.14 & 6.87 Hz, 3H). HPLC: Rt = 6.406 min following Method R. ES-MS: calcd. for $C_{26}H_{26}N_2O_4S$ (462.16) found: 461.2 [M-H].

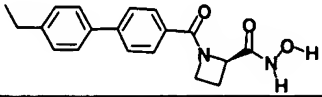
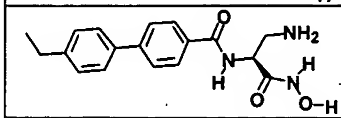
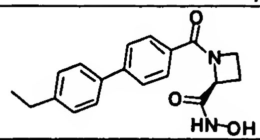
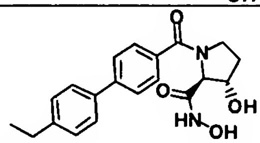
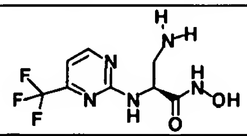
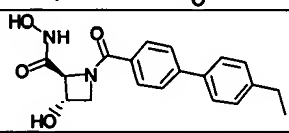
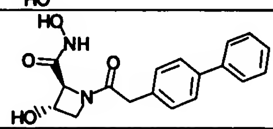
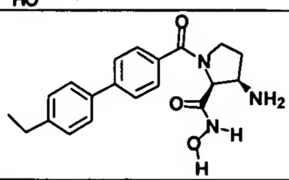
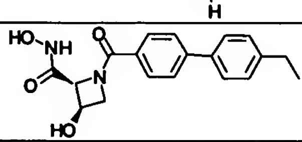
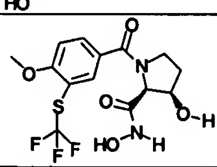
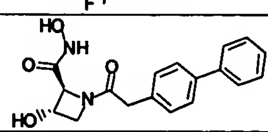
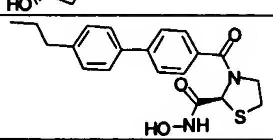
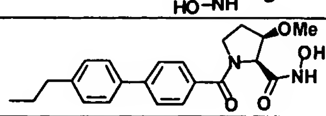
[00336] Step 5: (*S*)-*N*-(benzyloxy)3-(4'-ethoxybiphenylcarbonyl)-thiazolidinesulfone-2-carboxamide was prepared from (*S*)-*N*-(benzyloxy)3-(4'-ethoxybiphenylcarbonyl)-thiazolidine-2-carboxamide following Method S (yield = 48%). ^{1}H NMR (DMSO-d_6): 11.86 (bs, 1H), 8.08 – 7.86 (m, 6H), 7.75 – 7.55 (m, 5H), 7.23 – 7.20 (d, J = 8.79 Hz, 2H), 5.45 (bs, 1H), 5.21 (s, 2H), 4.27 – 4.24 (d, J = 7.14 Hz, 4H), 3.96 (bs, 1H), 3.71 (m, 1H), 1.55 – 1.51 (t, J = 6.87 Hz, 3H). HPLC: Rt = 6.317 min following Method R. ES-MS: calcd. for $C_{26}H_{26}N_2O_6S$ (494.15) found: 493.2 [M-H].

[00337] Step 6: (*S*)-3-(4'-ethoxybiphenylcarbonyl)-*N*-hydroxythiazolidinesulfone-2-carboxamide was prepared from (*S*)-*N*-(benzyloxy)3-(4'-ethoxybiphenylcarbonyl)-thiazolidinesulfone-2-carboxamide following Method P (yield = 20%). ^{1}H NMR (DMSO-d_6): 11.26 (bs, 1H), 9.46 (bs, 1H), 7.9 – 7.51 (m, 6H), 7.05 – 7.02 (d, J = 8.79 Hz, 2H), 5.3 (bs, 1H), 4.11 – 4.04 (dd, J = 6.87 Hz, 3H), 3.76 - 3.71 (m, 2H), 3.51 – 3.38 (m, 1H), 1.37 – 1.32 (t, J = 7.14 & 6.87 Hz, 3H). HPLC: Rt = 5.154 min following Method R. ES-MS: calcd. for $C_{19}H_{20}N_2O_6S$ (404.44) found: 403.2 [M-H].

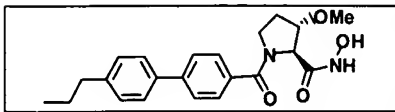
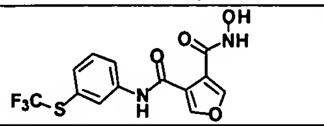
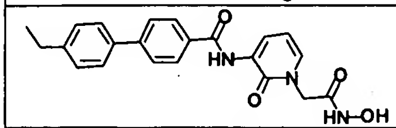
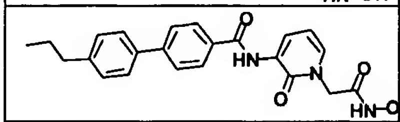
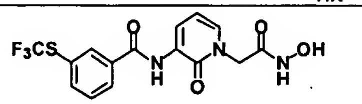
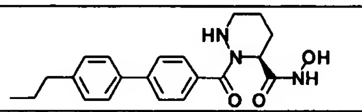
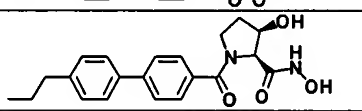
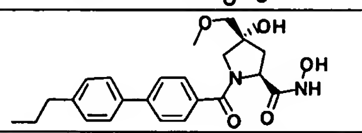
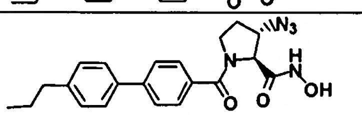
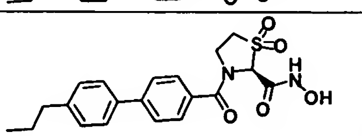
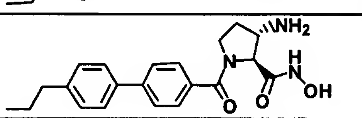
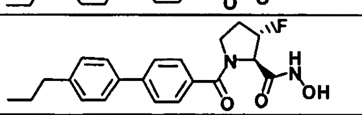
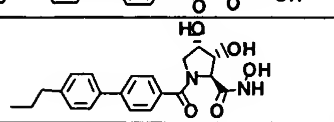
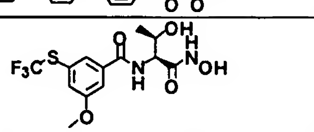
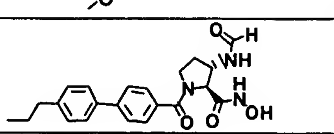
[00338] The following methods may be used to test compounds of this invention. Results are reproduced in **TABLE 1** below.

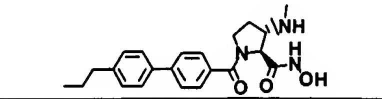
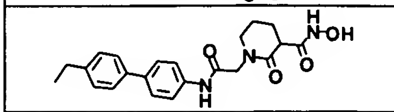
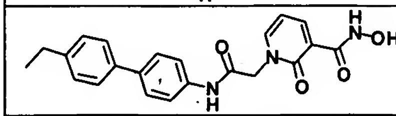
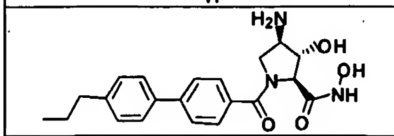
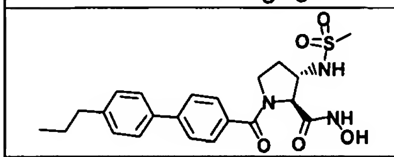
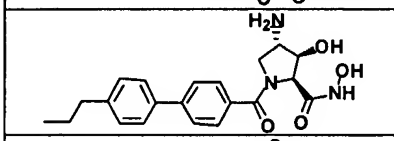
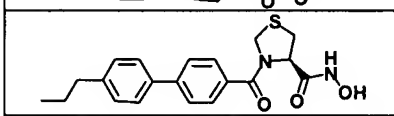
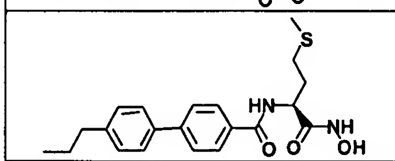
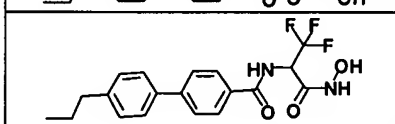
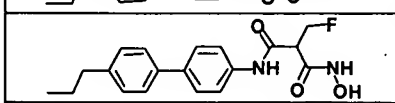
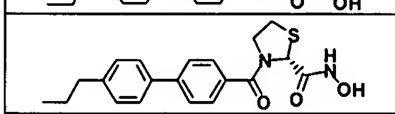
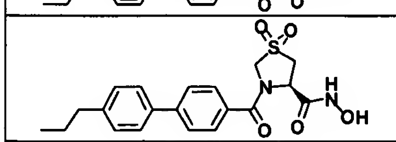
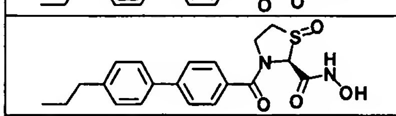
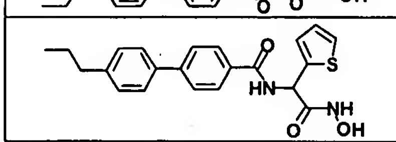
TABLE 1

Structure	E. coli (2)	E. coli tolC	P. aerug. (2)	P. aerug. Hypersuc	K. pneu.	H. influen.	ENZYME
	>64	64	>64	>64	>64	ND	No inhibition @ 10μg/ml

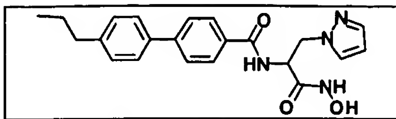
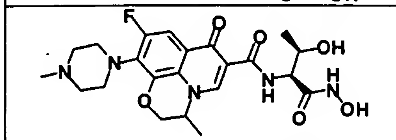
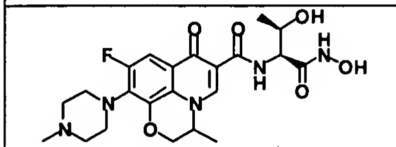
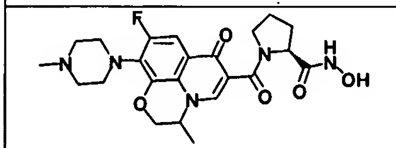
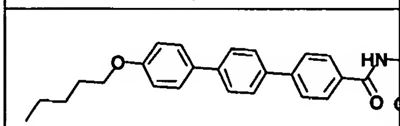
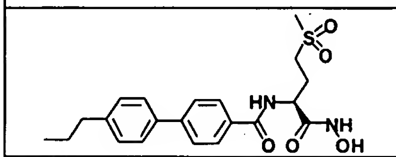
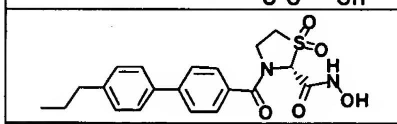
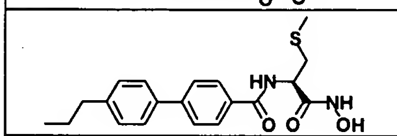
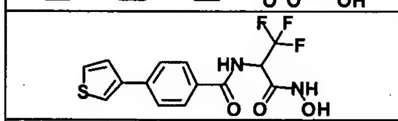
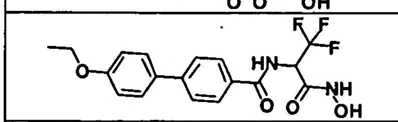
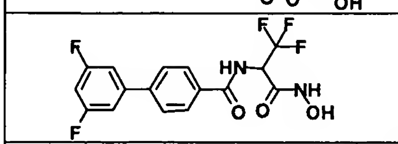
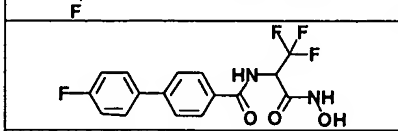
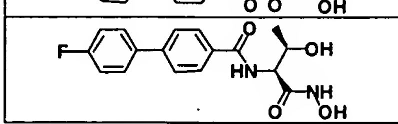
	>64	>64	>64	>64	>64	ND	85% (@10μg/ml)
	8-16	8	8	1	8	ND	92 (@10 μg/ml)
	>64	>64	>64	>64	>64	>64	72 (@10 μg/ml)
	>64	>64	>64	64	>64	>64	78.8 (@1 μg/ml)
	>64	>64	>64	>64	>64	>64	5 (@10 μg/ml)
	32->64	>64	>64	>64	>64	>64	53 (@10 μg/ml)
	>64	>64	>64	>64	>64	>64	48 (@10 μg/ml)
	>64	>64	16-32	64	>64	>64	93 (@0.5 μg/ml)
	>64	32	>64	64	>64	>64	51 (@10 μg/ml)
	>64	32	>64	>64	64	>64	52 (@10 μg/ml)
	>64	>64	>64	>64	>64	>64	50 (@10 μg/ml)
	>64	>64	64	16	32	64	71 (@10 μg/ml)
	>64	32	>64	>64	>64	64	21 (@10 μg/ml)

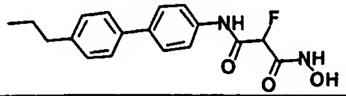
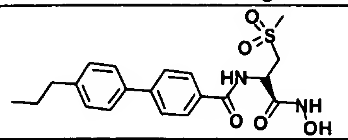
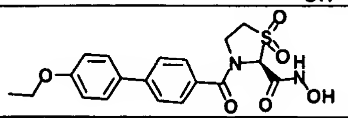
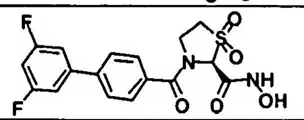
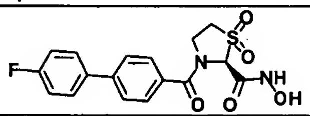
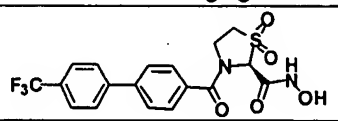
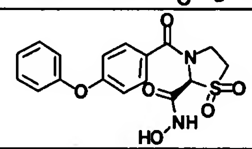
NB1:662111.3

	64->64	64	>64	64	64	>64	84 (@10 μg/ml)
	64->64	64	>64	>64	>64	>64	<10 (@10 μg/ml)
	>64	>64	>64	>64	>64	>64	<10 (@10 μg/ml)
	>64	>64	>64	>64	>64	>64	23 (@10 μg/ml)
	>64	>64	>64	>64	>64	>64	14 (@10 μg/ml)
	>64	32	>64	>64	>64	>64	No inhibition@0.5 μg/ml
	>64	64	64->64	4	>64	>64	95.2 (@1 μg/ml)
	>64	>64	>64	32	>64	>64	57 (@1 μg/ml)
	>64	32	>64	>64	>64	>64	35 (@0.5 μg/ml)
	16	2	8	2	4	32	41 (@0.1 μg/ml)
	64	32	64->64	64	64	16	65 (@0.5 μg/ml)
	>64	16	>64	32	32	>64	87 (@0.5 μg/ml)
	>64	64	>64	64	>64	>64	60 (@0.5 μg/ml)
	32	8	>64	>64	>64	>64	<10 (@0.5 μg/ml)
	>64	32	>64	64	>64	>64	69 (@0.5 μg/ml)

	64	32	>64	64	>64	32	29 (@0.5 μg/ml)
	>64	>64	>64	>64	>64	>64	<10 (@0.5 μg/ml)
	>64	>64	>64	>64	>64	>64	<10 (@0.5 μg/ml)
	>64	32	64	16	>64	32	84 (@0.5 μg/ml)
	>64	32	>64	>64	>64	>64	55 (@0.5 μg/ml)
	>64	>64	32->64	8	>64	32	95 (@0.5 μg/ml)
	>64	16	>64	16	>64	>64	57 (@0.5 μg/ml)
	>64	>64	>64	>64	>64	>64	72 (@0.5 μg/ml)
	0.5	0.25	16	1	0.5	0.25	<10 (@0.1 μg/ml)
	16-32	4	>64	16	8	8	77 (@0.5 μg/ml)
	>64	16	>64	32	32	64	50 (@0.5 μg/ml)
	32->64	8	16	2	16	>64	98 (@0.5 μg/ml)
	>64	16	32	8	64	>64	99 (@0.5 μg/ml)
	64	2	>64	32	8	16	87 (@0.5 μg/ml)

NB1:662111.3

	>64	1	>64	64	>64	>64	100 (@0.5 µg/ml)
	>64	>64	>64	>64	>64	>64	<10 (@0.1 µg/ml)
	>64	>64	>64	>64	>64	>64	<10 (@0.1 µg/ml)
	>64	64	>64	>64	>64	>64	<10 (@0.1 µg/ml)
	>64	>64	>64	>64	>64	>64	<10 (@0.1 µg/ml)
	>64	>64	>64	>64	>64	>64	38 (@0.1 µg/ml)
	8-16	2	8	2	4	32	10 (@0.1 µg/ml)
	>64	32	>64	>64	>64	>64	13 (@0.1 µg/ml)
	>64	16	32	2	>64	8	13 (@0.1 µg/ml)
	2	0.25	16-32	0.5	1	0.5	<10 (@0.1 µg/ml)
	16	8	8	2	16	16	24 (@0.1 µg/ml)
	8	4	8-16	2	16	4	12 (@0.1 µg/ml)
	32	8	16-32	8	64	32	58 (@0.1 µg/ml)

	>64	32	>64	>64	>64	>64	<10 (@0.1 µg/ml)
	>64	<=0.06	>64	32	4	>64	59 (@0.1 µg/ml)
	>64	<=0.06	4-16	2	32	16	12 (@0.1 µg/ml)
	>64	0.125	32-16	8	>64	>64	8 (@0.1 µg/ml)
	>64	<=0.06	4-32	2	>64	>64	32; 42 (@0.1 µg/ml)
	>64	<=0.06	32	8	>64	>64	30 (@0.1 µg/ml)
	>64	0.125	>64	>64	>64	>64	21 (@0.1 µg/ml)

Example A

Susceptibility Testing

[00339] Compounds were tested following the microdilution method of CLSI (Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard - sixth edition. CLSI document M7-A5, CLSI, Wayne, PA. 2003). Assays were performed in sterile plastic 96-well microtiter trays with round bottom wells (Greiner).

Compound Preparation

[00340] Stock solutions of test compounds and control antibiotics were prepared at 10mg/ml in DMSO. Serial 2-fold dilutions of each drug were performed in a microtiter plate across each row using DMSO as solvent at 100- fold the desired final concentration. Wells in columns #1-11 contain drug and column #12 was kept as a growth control for the organism with

no drug. Each well in the mother plate was diluted with sterile deionized water and DMSO, mixed, and volumes of 10 µl distributed to each well in the resulting assay plates.

Preparation of Inoculum

[00341] Stock cultures were prepared using the Microbank™ method (Pro-Lab Diagnostics) and stored at -80°C. To propagate each strain, one bead was removed from the frozen vial and aseptically streaked onto Trypticase Soy Agar (Difco) which were incubated at 35°C. Standardized inocula were prepared using the direct colony suspension method according to CLSI guidelines (Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard - sixth edition. CLSI document M7-A5, CLSI, Wayne, PA, 2003). Isolated colonies were selected from an 18-24 hr agar plate and resuspended in 0.9% sterile saline to match a 0.5 McFarland turbidity standard using a colorimeter (Vitek) at 80% of transmitance. The suspension was used within 15 minutes of preparation.

Escherichia coli VECO1003	*Escherichia coli* ATCC 25922
Escherichia coli VECO2096	*Escherichia coli* MG1655
Escherichia coli VECO2526 *tolC*	*Escherichia coli* MG1655 *tolC*
Enterobacter cloacae VECL1001	*Enterobacter cloacae* ATCC 35030
Klebsiella pneumoniae VKPN1001	*Klebsiella pneumoniae* ATCC 10031
Morganella morganii VMMO1001	*Morganella morganii* ATCC 25830
Pseudomonas aeruginosa VPAE1004	*Pseudomonas aeruginosa* ATCC 27853
Pseudomonas aeruginosa VPAE1010	*Pseudomonas aeruginosa* K799
Pseudomonas aeruginosa VPAE1011	K799/61 (Δ efflux, hypersusceptible strain)
Haemophilus influenzae VHIN1001	*Haemophilus influenzae ATCC 49247*
Staphylococcus aureus VSAU1001	*Staphylococcus aureus* ATCC 29213

Preparation of Assay Plates for MICs

[00342] Mueller-Hinton Broth MHB (Difco) was prepared at a 1.1X concentration and supplemented with Ca^{++} and Mg^{++} as recommended by CLSI. For each organism, the standardized suspension was diluted 1:180 into appropriate growth medium in a sterile reservoir. After mixing, wells in the drug-containing assay plates were inoculated with a volume of 90µl. Thus, for each MIC determination, each well contains a final volume of 100 µl with an inoculum size of approximately 5×10^5 cfu/ml and no more than 1% DMSO.

Interpretation of MIC

[00343] The completed microtiter plates were incubated 20 h at 35oC in ambient air. Optical density of each well was determined at 600 nm using a VersaMax Microplate reader (Molecular Devices, Sunnyvale, CA). The MIC was defined as the lowest drug concentration causing complete suppression of visible bacterial growth.

Example B

Efficacy in Murine *E. coli* Septicemia

[00344] Efficacy studies were performed in an *E. coli* murine septicemia model according to models published elsewhere (Goldstein, B. P., G. Candiani, T. M. Arain, G. Romano, I. Ciciliato, M. Berti, M. Abbondi, R. Scotti, M. Mainini, F. Ripamonti, and et al. 1995. Antimicrobial activity of MDL 63,246, a new semisynthetic glycopeptide antibiotic Antimicrob Agents Chemother. 39:1580-1588.; Misiek, M., T. A. Pursiano, F. Leitner, and K. E. Price 1973. Microbiological properties of a new cephalosporin, BL-S 339: 7-(phenylacetimidoyl-aminoacetamido)-3-(2-methyl-1,3,4-thiadiazol-5-ylthio methyl)ceph-3-em-4-carboxylic acid Antimicrob Agents Chemother. 3:40-48).

Compound preparation

[00345] The compound was dissolved in 10% DMSO, 0.1% Tween 80, 0.9% NaCl solution and administered intravenously at 10 ml/kg at 1 hour after bacterial inoculation. The compound was administered at 80, 40, 20, 5, 2.5, and 1.25 mg/kg. A control with ampicillin was included in the evaluation.

Efficacy model

[00346] Male or female ICR mice weighing 22±2 g from MDS Pharma Services were used for the evaluation. Food and water was given ad libitum. Groups of 6 mice weighing 22 ± g were used for the experiment. Mice were inoculated intraperitoneally with *Escherichia coli* ATCC 25922 at 4×10^4 CFU in 0.5 ml of Brain Heart Infusion Broth (Difco) containing 5% mucin (Sigma). Mortality was recorded once daily for 7 days following bacterial inoculation. The ED50 was determined by non-linear regression and is 28.3 for the compound and 14.1 for ampicillin.

Enzyme Inhibition Testing

[00347] Compounds were tested based on a published method (Wang W., **2001**, Anal Biochem, *290*, 338-46) with modifications. Enzyme assays were performed in the assay buffer (50mM HEPES, pH8, 0.005%Brij, 50 µM $ZnSO_4$, 1 mg/ml BSA) in 96-well V-bottom microtiter plates.

Compound preparation

[00348] Stock solutions of test compounds and control antibiotics are prepared at 10mg/ml in DMSO and are diluted in the assay buffer to 6- fold the final testing concentration. 5µl compound dilution is distributed to the well of the assay plate. EDTA is used as positive control and the final concentration in assay is 12.5 mM.

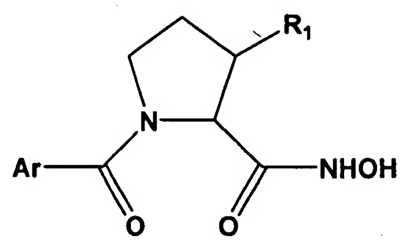
Enzyme inhibition assay

[00349] *P. ae* LpxC enzyme dilution in the assay buffer is added to the compound in plate and pre-incubated with the compound at room temperature for 10 min. LpxC substrate is added to initiate the enzyme reaction and the final enzyme and substrate concentrations are 1.2 μM and 0.4 mM, respectively. The reaction continues at RT for 4 hrs before diluted with 45μl of Borate buffer (0.4 M, pH9), followed by addition of 40μl derivatization reagent (fluorescamine 2mg/ml DMF). This mixture is incubated at RT for 10min followed by addition of 150μl DMF/H2O (1:1). The resulting solution is loaded onto Millipore filter unit (Microcon 10k MWCO) and spun at 13k rpm on bench top centrifuge for 15min. 100 μl of this filtrate is transferred to a low fluorescence clear-bottom 96-well plate (Corning) and the fluorescence is detected at ex360nm and em465nm on a Tecan fluorescence plate reader. The percent inhibition is calculated based on EDTA produces 100% inhibition and negative control produces 100% activity.

[00350] While the invention has been described and illustrated herein by references to various specific material, procedures and examples, it is understood that the invention is not restricted to the particular material combinations of material, and procedures selected for that purpose. Numerous variations of such details can be implied as will be appreciated by those skilled in the art.

WHAT IS CLAIMED:

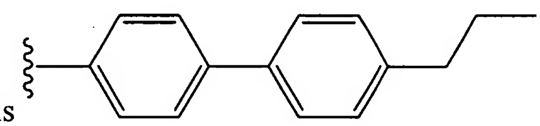
1. A compound of Formula I:



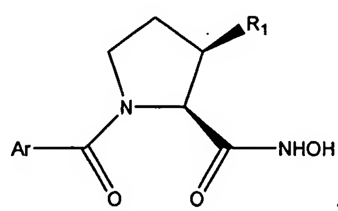
I

wherein R_1 is selected from the group consisting of N_3, NH_2, $NHSO_2CH_3$, NHCOH, $NHCH_3$, F, and OCH_3; and

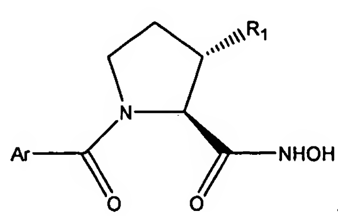
wherein Ar is an optionally substituted aryl or heteroaryl.

2. The compound of claim 1, wherein Ar is  .

3. The compound of claim 1, having the following structure:



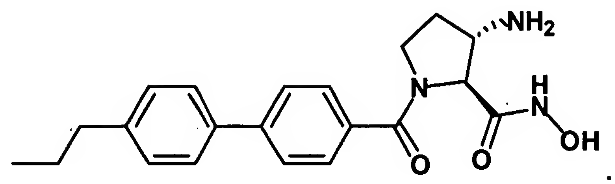
4. The compound of claim 1, having the following structure:



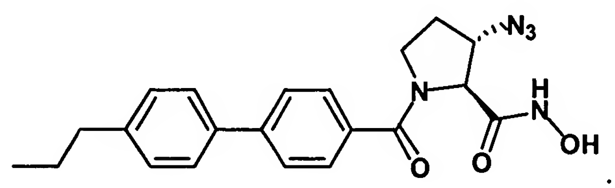
5. The compound of claim 1, wherein R_1 is NH_2.

NB1:662111.3

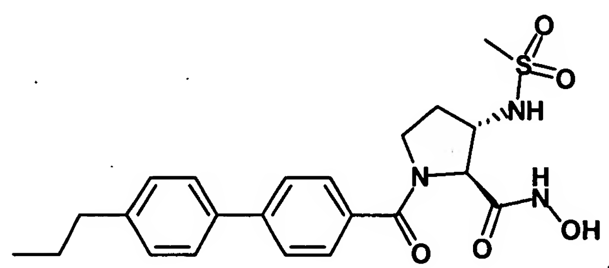
6. The compound of claim 1, having the following structure:



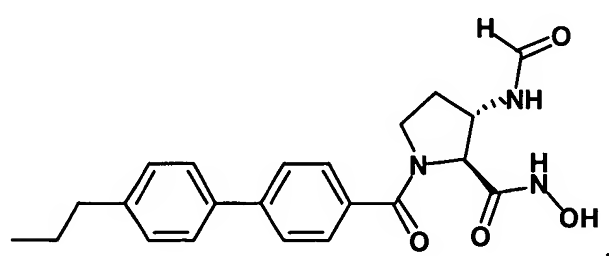
7. The compound of claim 1, having the following structure:



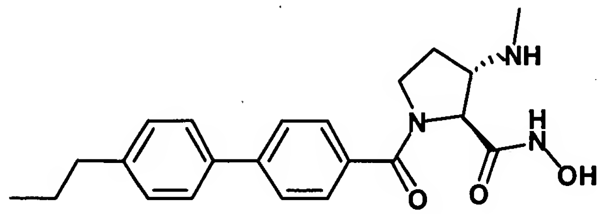
8. The compound of claim 1, having the following structure:



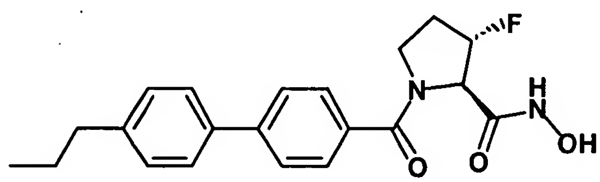
9. The compound of claim 1, having the following structure:



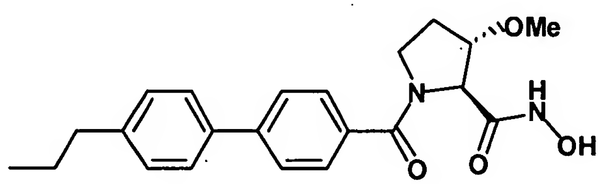
10. The compound of claim 1, having the following structure:



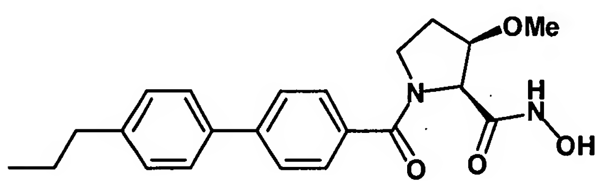
11. The compound of claim 1, having the following structure:



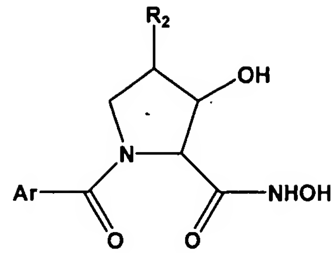
12. The compound of claim 1, having the following structure:



13. The compound of claim 1, having the following structure:



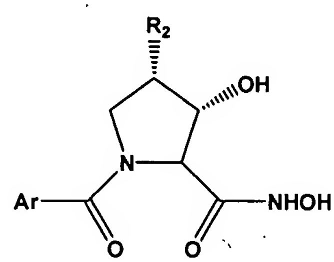
14. A compound of formula II:



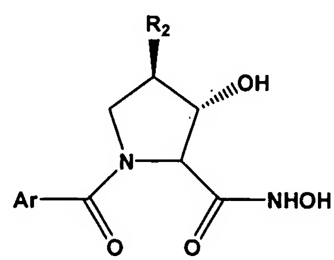
II

wherein R_2 is selected from the group consisting of OH and NH_2; and wherein Ar is an optionally substituted aryl or heteroaryl.

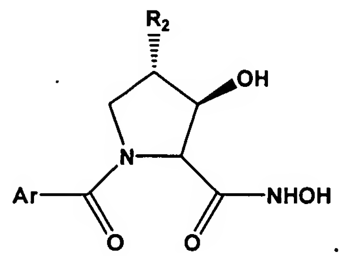
15. The compound of claim 14, having the following structure:



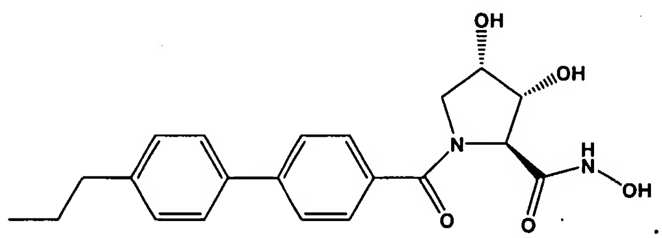
16. The compound of claim 14, having the following structure:



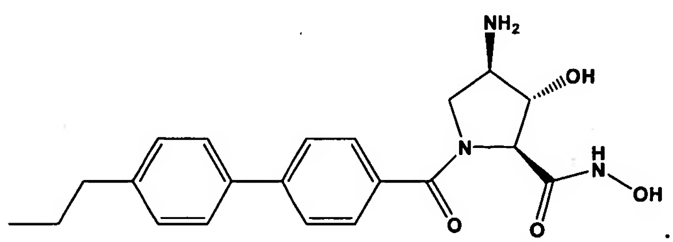
17. The compound of claim 14, having the following structure:



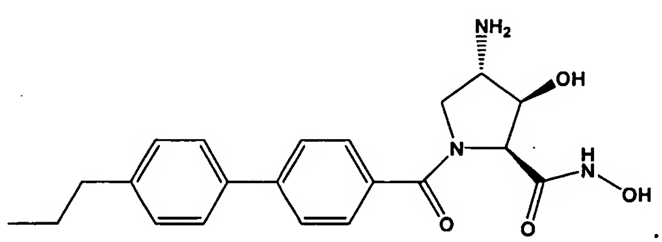
18. The compound of claim 14, having the following structure:



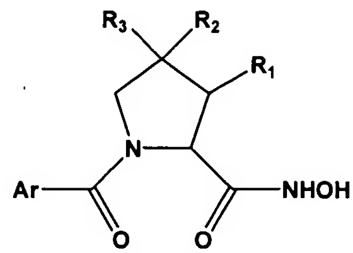
19. The compound of claim 14, having the following structure:



20. The compound of claim 14, having the following structure:



21. A compound of Formula III:



III

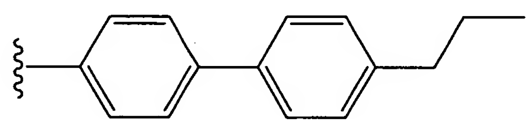
wherein R_1 is selected from the group consisting of H, N_3, NH_2, $NHSO_2CH_3$, NHCOH, $NHCH_3$, F, OCH_3, and OH;

R_2 is selected from the group consisting of H, OH, and NH_2;

R_3 is selected from the group consisting of H and CH_2OCH_3; and

Ar is an optionally substituted aryl or heteroaryl.

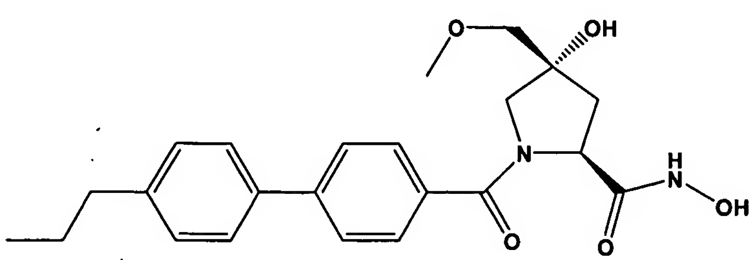
22. The compound of claim 21, wherein Ar is



23. The compound of claim 21, wherein R_1 is NH_2, R_2 is H, and R_3 is H.

24. The compound of claim 21, wherein R_1 is H, R_2 is OH, and R_3 is CH_2OCH_3.

25. The compound of claim 21, having the following structure



26. The compound of claim 21, wherein R_1 is N_3, R_2 is H, and R_3 is H.

27. The compound of claim 21, wherein R_1 is $NHSO_2CH_3$, R_2 is H, and R_3 is H.

28. The compound of claim 21, wherein R_1 is NHCOH, R_2 is H, and R_3 is H.

29. The compound of claim 21, wherein R_1 is $NHCH_3$, R_2 is H, and R_3 is H.

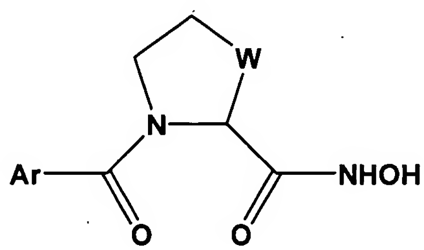
30. The compound of claim 21, wherein R_1 is F, R_2 is H, and R_3 is H.

31. The compound of claim 21, wherein R_1 is OCH_3, R_2 is H, and R_3 is H.

32. The compound of claim 21, wherein R_1 is OH, R_2 is OH, and R_3 is H.

33. The compound of claim 21, wherein R_1 is OH, R_2 is NH_2, and R_3 is H.

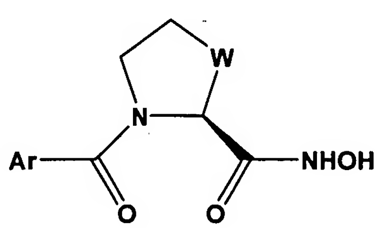
34. A compound of Formula IV:



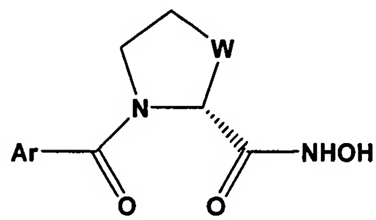
IV

wherein W is selected from the group consisting of S, SO, and SO_2; and
Ar is an optionally substituted aryl or heteroaryl.

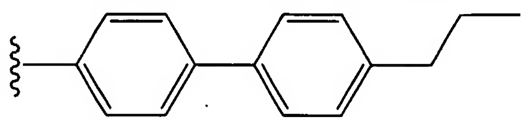
35. The compound of claim 34, having the following structure:

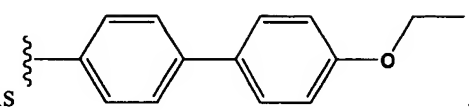


36. The compound of claim 34, having the following structure:



37. The compound of claim 34, wherein Ar is



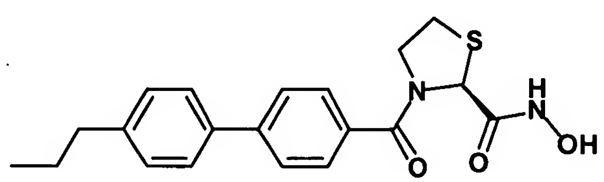
38. The compound of claim 34, wherein Ar is 

39. The compound of claim 34, wherein W is SO_2.

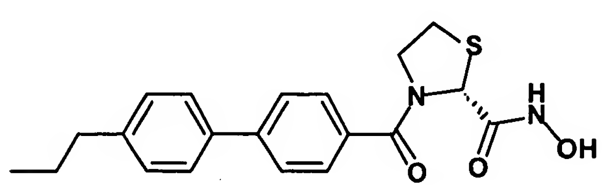
40. The compound of claim 34, wherein W is S.

41. The compound of claim 34, wherein W is SO.

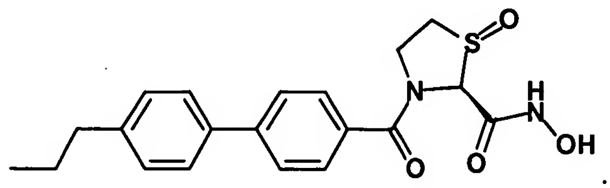
42. The compound of claim 34, having the following structure:



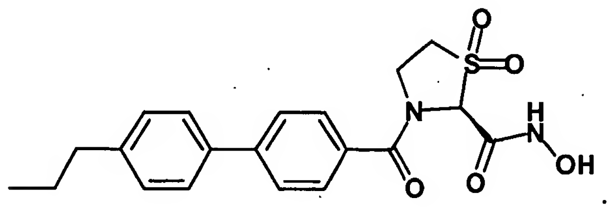
43. The compound of claim 34, having the following structure:



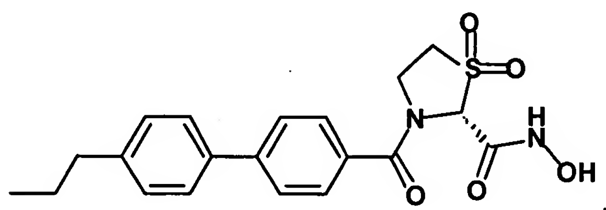
44. The compound of claim 34, having the following structure:



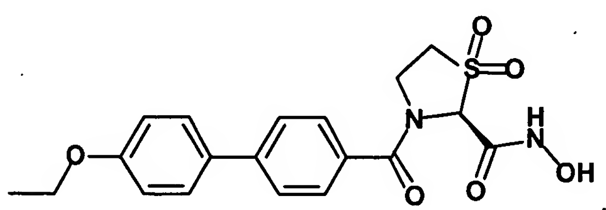
45. The compound of claim 34, having the following structure:



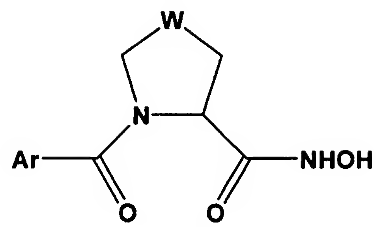
46. The compound of claim 34, having the following structure:



47. The compound of claim 34, having the following structure:



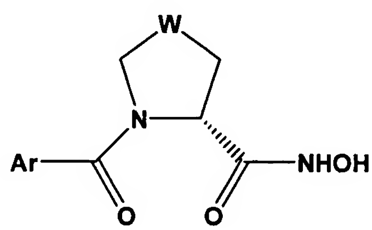
48. A compound of Formula V:



V

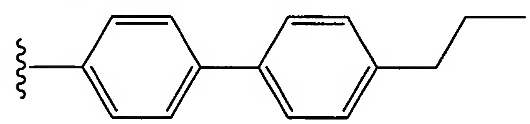
wherein W is selected from the group consisting of S and SO_2; and Ar is an optionally substituted aryl or heteroaryl.

49. The compound of claim 48, having the following structure:



.

50. The compound of claim 48, wherein Ar is

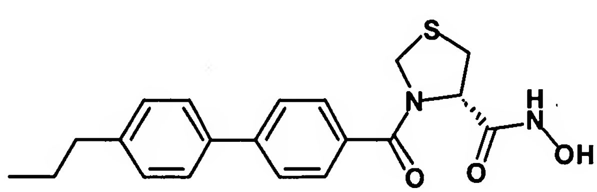


.

51. The compound of claim 50, wherein W is S.

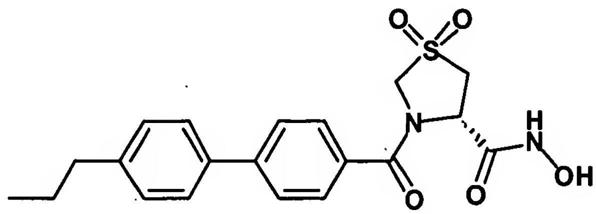
52. The compound of claim 50, wherein W is SO_2.

53. The compound of claim 48, having the following structure:

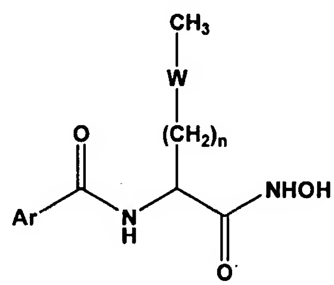


.

54. The compound of claim 48, having the following structure:



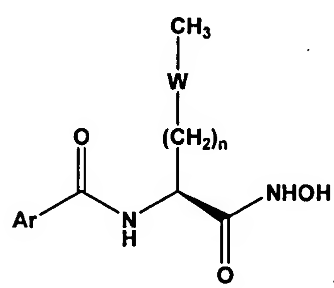
55. A compound of Formula VI:



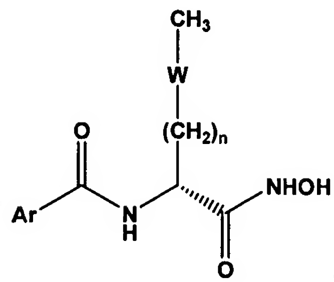
VI

wherein W is selected from the group consisting of S and SO_2;
n is 1 or 2; and
Ar is an optionally substituted aryl or heteroaryl.

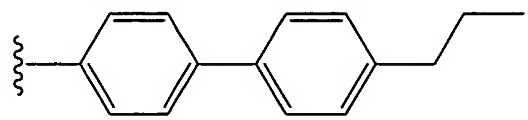
56. The compound of claim 55, having the following structure:



57. The compound of claim 55, having the following structure:



58. The compound of claim 55, wherein Ar is



59. The compound of claim 58, wherein W is S.

60. The compound of claim 58, wherein W is SO_2.

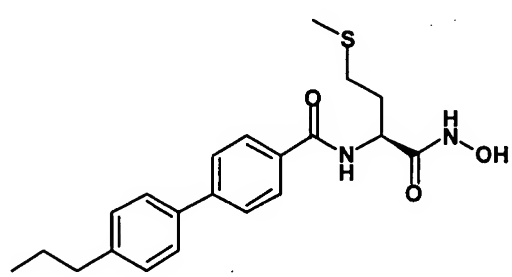
61. The compound of claim 55, wherein W is S and n is 1.

62. The compound of claim 55, wherein W is S and n is 2.

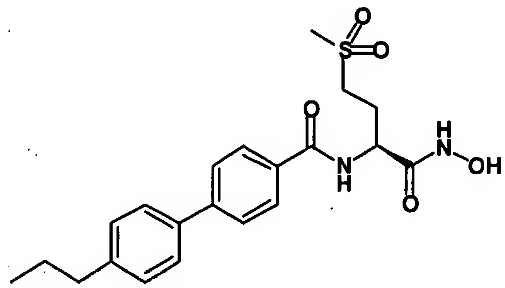
63. The compound of claim 55, wherein W is SO_2 and n is 1.

64. The compound of claim 55, wherein W is SO_2 and n is 2.

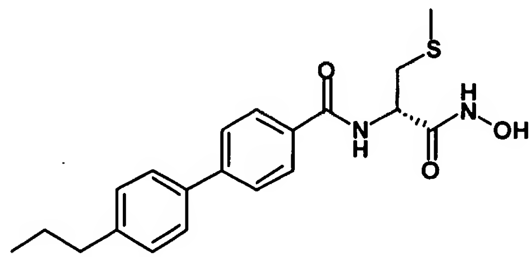
65. The compound of claim 55, having the following structure:



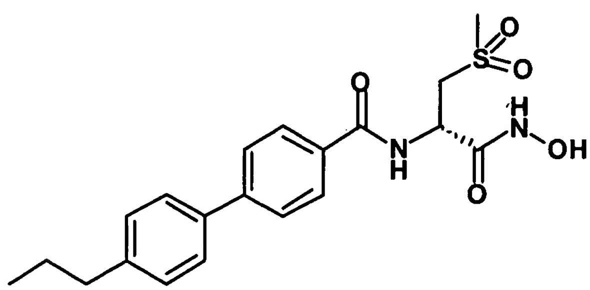
66. The compound of claim 55, having the following structure:



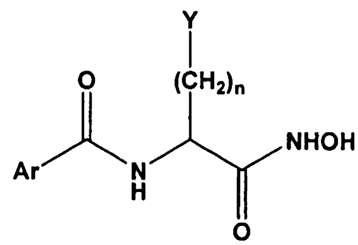
67. The compound of claim 55, having the following structure:



68. The compound of claim 55, having the following structure:



69. A compound of Formula VII:



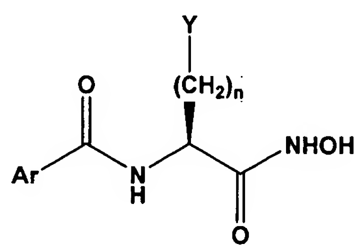
VII

wherein Y is a heteroaryl;

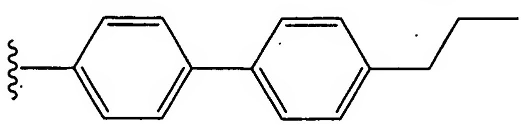
n is 0 or 1; and

Ar is an optionally substituted aryl or heteroaryl.

70. The compound of claim 69, having the following structure:

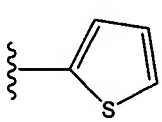
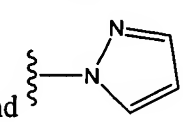


71. The compound of claim 69, wherein Ar is

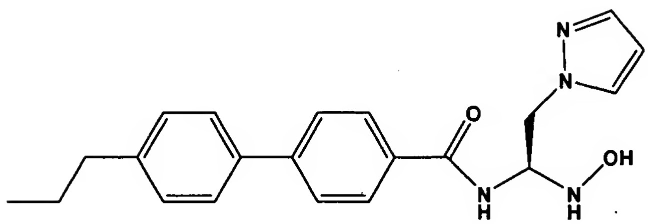


72. The compound of claim 69, wherein Y is a 5-membered heteroaryl ring.

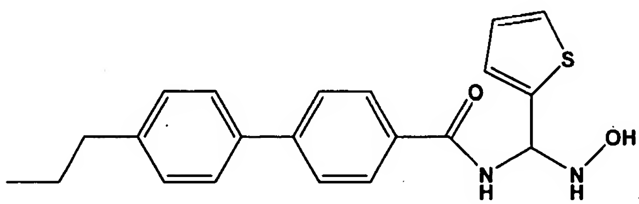
73. The compound of claim 69, wherein Y is selected from the group consisting of

 and .

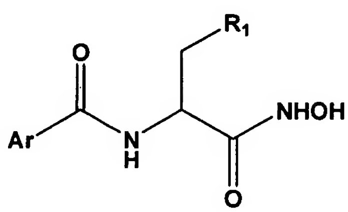
74. The compound of claim 69, having the following structure:



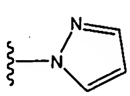
75. The compound of claim 69, having the following structure:



76. A compound of Formula VIII:

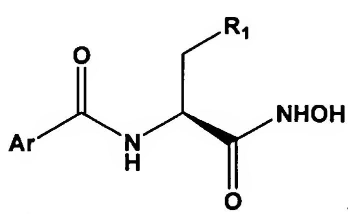


VIII

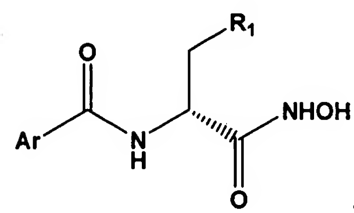
wherein R_1 is selected from the group consisting of CH_2SCH_3, $CH_2SO_2CH_3$, SCH_3, SO_2CH_3, and ; and

Ar is an optionally substituted aryl or heteroaryl.

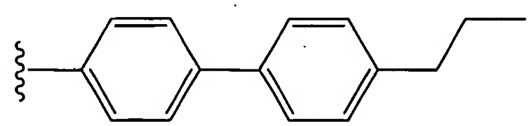
77. The compound of claim 76, having the following structure:



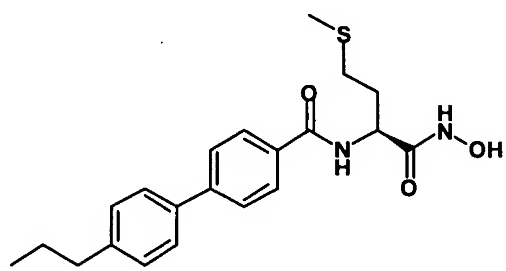
78. The compound of claim 76, having the following structure:



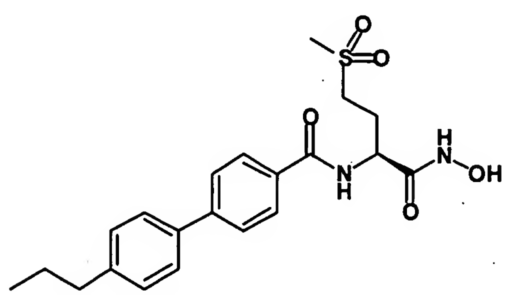
79. The compound of claim 76, wherein Ar is



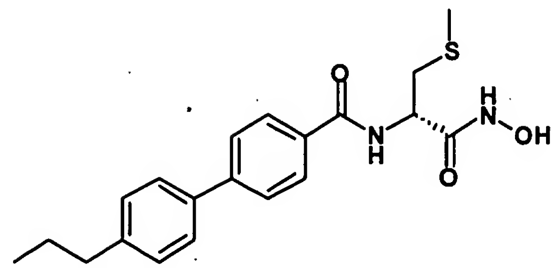
80. The compound of claim 76, having the following structure:



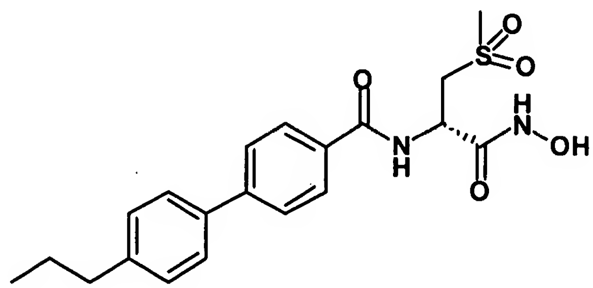
81. The compound of claim 76, having the following structure:



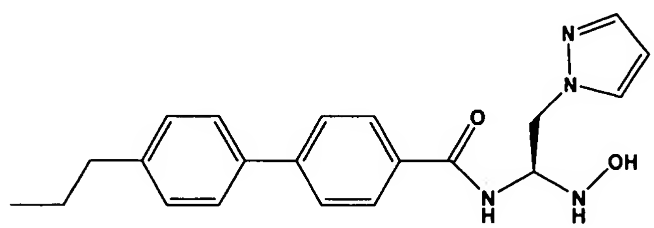
82. The compound of claim 76, having the following structure:



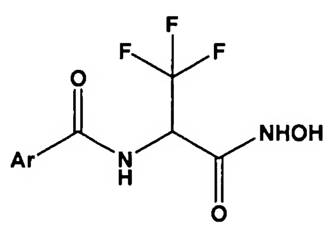
83. The compound of claim 76, having the following structure:



84. The compound of claim 76, having the following structure:

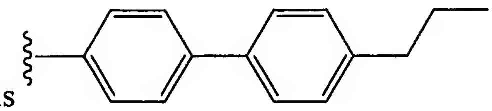


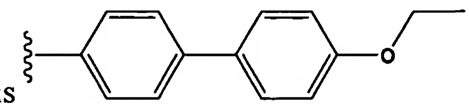
85. A compound of Formula IX:

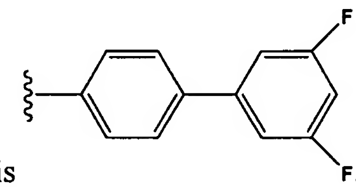


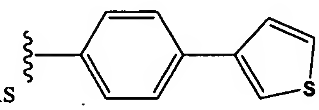
IX

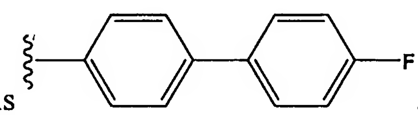
wherein Ar is an optionally substituted aryl or heteroaryl.

86. The compound of claim 85, wherein Ar is  .

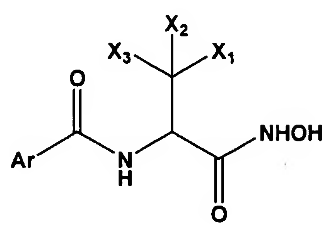
87. The compound of claim 85, wherein Ar is  .

88. The compound of claim 85, wherein Ar is  .

89. The compound of claim 85, wherein Ar is  .

90. The compound of claim 85, wherein Ar is  .

91. A compound of Formula X:

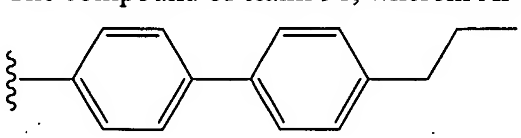


X

wherein X_1, X_2, and X_3 are each independently selected from the group consisting of H and F; and

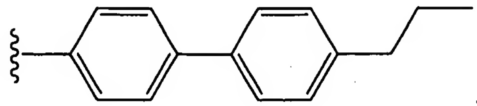
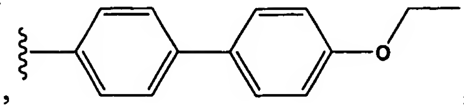
Ar is an optionally substituted aryl or heteroaryl.

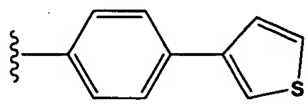
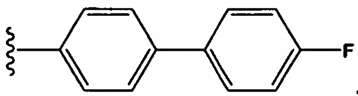
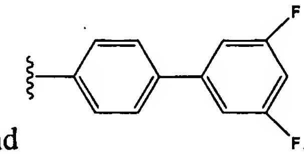
92. The compound of claim 91, wherein Ar is



.

93. The compound of claim 91, wherein Ar is selected from the group consisting of

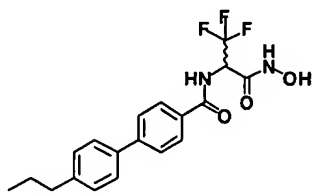
, ,

, , and .

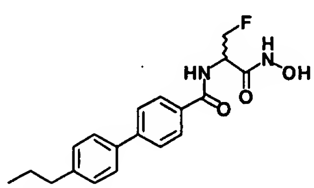
94. The compound of claim 91, wherein X_1, X_2, and X_3 are F.

95. The compound of claim 91, wherein X_1 is F, X_2 is H, and X_3 is H.

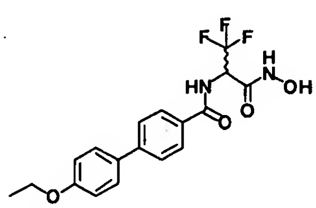
96. The compound of claim 91, having the following structure:



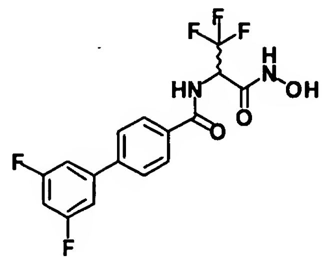
97. The compound of claim 91, having the following structure:



98. The compound of claim 91, having the following structure:

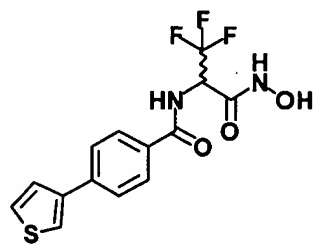


99. The compound of claim 91, having the following structure:



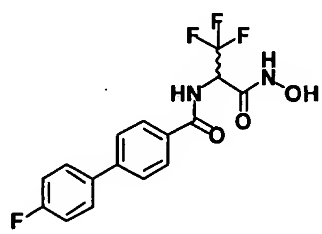
.

100. The compound of claim 91, having the following structure:



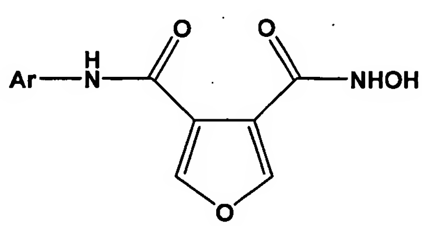
.

101. The compound of claim 91, having the following structure:



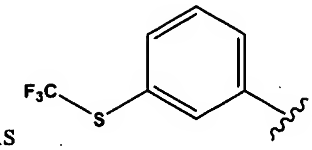
.

102. A compound of Formula XI:

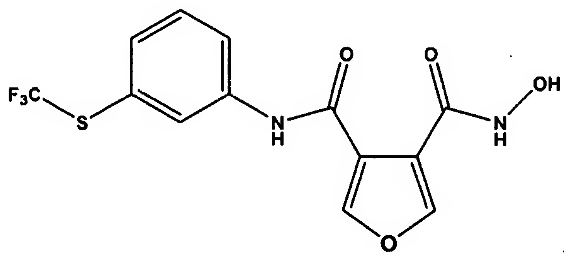


XI

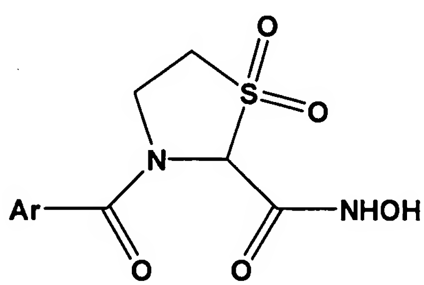
wherein Ar is an optionally substituted aryl.

103. The compound of claim 102, wherein Ar is .

104. The compound of claim 102, having the following structure:

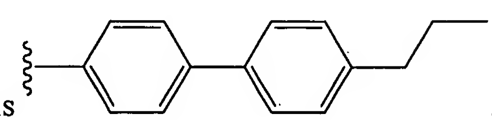


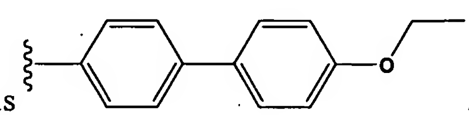
105. A compound of Formula XII:



XII

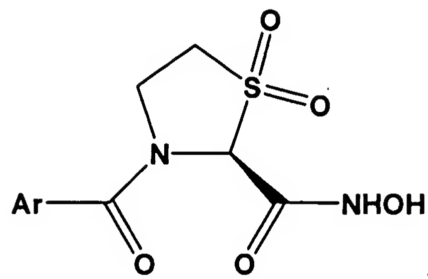
wherein Ar is an optionally substituted aryl or heteroaryl.

106. The compound of claim 105, wherein Ar is .

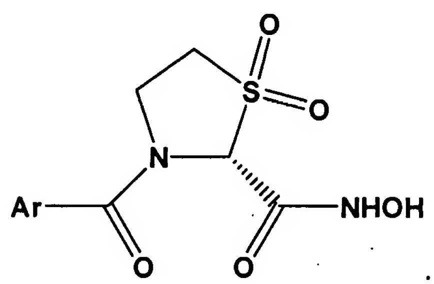
107. The compound of claim 105, wherein Ar is .

NB1:662111.3

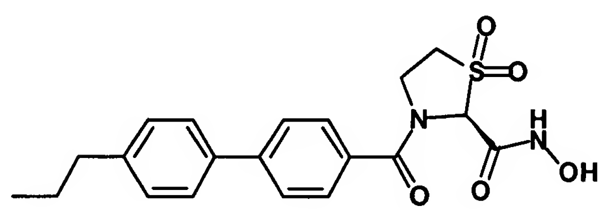
108. The compound of claim 105, having the following structure:



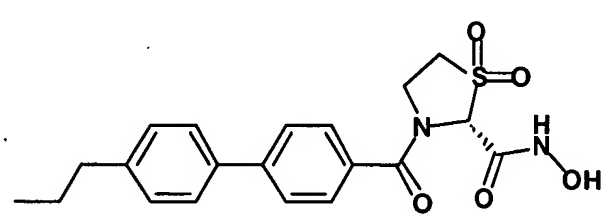
109. The compound of claim 105, having the following structure:



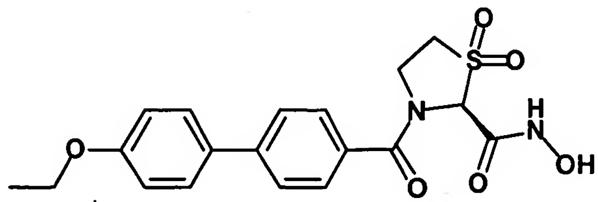
110. The compound of claim 105, having the following structure:



111. The compound of claim 105, having the following structure:



112. The compound of claim 105, having the following structure:



ABSTRACT

Novel N-hydroxyamide derivatives are disclosed. These N-hydroxyamide derivatives inhibit UPD-3-*O*-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase, an enzyme present in gram negative bacteria and are therefore useful as antimicrobials and antibiotics. Methods of synthesis and of use of the compounds are also disclosed.